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PERIPHERAL NEUROPATHY CAUSED BY ARSENICAL INTOXICATION*

A Study of 41 Cases with Observations on the Effects of BAL (2,3, Dimercapto-Propanol)

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EARLY in the present century lesions of the peripheral nerves caused by arsenical intoxication were a frequent occurrence. In most cases the neuropathy could be attributed to contact with the many household articles such as dyes, wallpaper and insecticides that contained large quantities of arsenic. In recent years, exposure to arsenic has been greatly reduced, and arsenical intoxication is no longer considered a common cause of peripheral neuropathy. Dusts and sprays containing arsenic, however, continue to be extensively employed as pesticides on farms in North Carolina, and their accidental ingestion or inhalation has produced numerous cases of poisoning. Our experience with this condition suggests that arsenical intoxication may be a more frequent cause of neuropathy, particularly in rural areas, than is generally realized. The present paper analyzes 41 cases of acute and chronic arsenical poisoning with peripheral neuropathy seen in Duke University Hospital and Durham Veterans Administration Hospital during the past fifteen years. The clinical and laboratory diagnosis of this condition is emphasized. Special attention is also given to the effects of BAL therapy of the neuropathy since there is little information on the value of this commonly recommended agent.

PRESENT SOURCES OF ARSENIC

Most of the cases of arsenical intoxication reported in the literature are caused by accidental ingestion of household or garden pesticides containing arsenous oxide, copper acetoarsenite (Paris green) or calcium or lead arsenate. Drugs containing arsenic such as sodium cacodylate, Fowler's solution and the arsphenamines were once a common cause of intoxication but are seldom employed at present. Toxic amounts of arsenic have also been ingested from consumption of fruits and vegetables that have been sprayed with insecticides containing calcium or lead arsenate. Orchardists in the habit of eating apples sprayed with lead arsenate have been found to ingest as much as 6.8 mg. of arsenic a day and to excrete up to 2.4 mg. in the urine in twenty-four hours, without any signs of intoxication.[1] On the other hand as little as 30 mg. of arsenous oxide can be fatal.[2] Individual susceptibility to arsenical intoxication has been known to vary considerably and seems to depend largely on the amount and duration of previous exposure.

Poisoning from industrial exposure to arsenic has been reported in a variety of industries, but such cases are infrequent. Poisoning from bootlegged whisky contaminated with arsenic continues to occur. The Manchester epidemic, affecting several thousand persons in the early 1900's, was traced to beer that had been brewed with dextrose and invert sugar contaminated with arsenic. Much present information regarding the clinical aspects of arsenical intoxication is based on studies of this British episode.[3] Arsenical poisoning from criminal intent was a popular form of homicide in the Middle Ages and continues to appear occasionally in areas where the poison is easily obtained.

LABORATORY DIAGNOSIS OF ARSENICAL POISONING

After absorption from the skin or mucous membranes, arsenic is deposited in the liver, spleen and kidneys. It also has a predilection for the keratin tissues. The concentration in the hair surpasses that of other tissues, and high levels have been detected many months after exposure[4]; the concentration depends on the portion of hair tested, the rate of hair growth, the quantity of arsenic absorbed and the

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duration of exposure, as well as the interval after the poisoning. The proximal portions of the hair have been found to contain arsenic within thirty hours of ingestion.[5] Recent studies of normal subjects have shown an average of 0.05 mg. calculated as arsenic trioxide per 100 gm. of hair, with a range of 0.025 to 0.088 mg.[6] Higher levels have also been found occasionally, but it seems safe to state that the normal value of arsenic is less than 0.1 mg. per 100 gm. of hair. In chronic poisoning, the concentration usually ranges from 0.1 mg. to 0.5 mg. per 100 gm. of hair

TABLE 1. *Distribution of 41 Cases of Arsenical Neuropathy According to Year of Onset.**

YEAR OF ONSET	NO. OF CASES
1937	1
1939	2
1941	4
1942	3
1943	2
1947	3
1948	7
1949	1
1950	5
1951	1
1952	4
1953	4
1954	4

*No cases found in years omitted from chronologic table.

whereas in acute cases as much as 1 to 3 mg. has been found several weeks after exposure.[5]

Confirmation of absorption of arsenic is usually based on the measurement of the twenty-four-hour urinary excretion. The concentration of urinary arsenic that can be considered to be evidence of poisoning will vary with the occupation of the patient, the area in which he lives and the type of food ingested. Normal persons without known exposure have been found to excrete an average of 0.015 mg. of arsenic per liter of urine, and those ingesting fruit sprayed with lead arsenate had values of 0.05 mg. per liter.[7] Repeated studies in our laboratory have led us to accept values less than 0.04 mg. per twenty-four-hour urine as normal, whereas others have found the usual values in normal persons to be between 0.01 and 0.06 mg. per liter of urine.[8] Although the exact level of urinary arsenic indicative of poisoning cannot be established, the majority of patients with clinical evidence of arsenical intoxication have values greater than 0.1 mg. per twenty-four-hour urinary excretion.[9,10]

CLINICAL MATERIAL

The material for this study consists of 41 patients who were treated for arsenical polyneuropathy at either Duke Hospital or the Durham Veterans Administration Hospital during the period 1937 through 1954. The principal criterion for selection of these cases was the presence of levels in the urine greater than 0.1 mg. of arsenic per twenty-four hours. Confirmatory evidence of intoxication was obtained in 11 patients by analysis of hair or visceral organs at autopsy. The technic employed in our laboratory for detection of arsenic is based on the Gutzeit method as outlined by Kolmer.[11] All the values used in this study are in terms of metallic arsenic. Patients who manifested neuritis caused by medications containing arsenic (Fowler's solution or the arsphenamines) were not included in this study. Three patients died shortly after the development of the neuritis, and the autopsy findings in these cases are considered. Biopsies of peripheral nerves were taken in 7 patients.

EPIDEMIOLOGIC DATA

The exact source of exposure to arsenic could not be definitely determined in many cases. For this reason an analysis was made for age, sex, race, occupation, seasonal onset and other data that might provide information of epidemiologic significance.

All the patients were between seventeen and sixty-seven years of age. Twenty-three patients were white men, and 3 were white women. There were 13 Negroes and 2 Negresses. Almost all the patients were in the lower economic groups and were treated on the public wards of Duke Hospital. A few were private patients, however. Only 1 patient resided in an urban area; the remainder lived in rural sections or small towns.

TABLE 2. *Sources of Arsenic in 41 Patients with Polyneuropathy.*

SOURCE	NO. OF CASES
Known:	
Accidental ingestion	4
Homicide	1
Probable:	
Arsenate spray	7
Illegal alcohol	5
Undetermined:	
Farm workers	14*
Other occupations	10

*Seven of these had chronic alcoholism.

The distribution of the patients according to the year of the onset of the disease is shown in Table 1. Eighteen of the cases in this study occurred during the past five years. This does not necessarily represent a true increase in the incidence of the illness but may indicate an improvement in clinical recognition. It is of interest that in 19 patients the illness began in the summer months, when arsenical compounds are used most extensively.

EXPOSURE

The analysis of the sources of exposure to arsenic is shown in Table 2. Four patients swallowed arsenic by

accident; 2 of them had mistaken a bottle of rat poison for whisky or mineral oil, and the others had eaten food that had allegedly been contaminated with arsenic. In 1 patient the diagnosis of arsenical intoxication was not made until autopsy. Several months later, his wife confessed that she had poisoned him.

The illness in 7 cases was probably due to direct contact with arsenate sprays or dusts. Most of these patients worked on tobacco farms and noted the onset of nausea and vomiting within twenty-four hours of the time they had sprayed their plants with arsenical mixtures. One of them soaked his clothes with the spray and became ill on the following day. In several cases more than 1 member of the family was affected at the same time. Another patient worked in a general store and lifted lead-arsenate dust from a large barrel to break it up into small amounts for sale.

Bootlegged whisky contaminated with arsenic may have been the source of poisoning in 5 cases. Nausea and vomiting developed while these patients were on an alcoholic debauch, peripheral neuropathy appearing shortly thereafter. The intoxication, however, may have been caused by contaminated containers or by accidental ingestion while the patients were inebriated.

The source of poisoning could not be determined in the remaining 24 patients. It was of interest that 14 of them were farmers who had used arsenical sprays at one time or other but could not relate the onset of their illness to a particular contact with this material. Seven of the farmers also had chronic alcoholism and drank illegal whisky, but no time relation between the onset of the illness and the ingestion of the alcoholic material could be established. There were no clues whatsoever to the source of arsenic in the 10 remaining patients. These patients were employed as sawmill or textile workers or as grocers, automobile mechanics and white-collar workers, and none of them gave a history of contact with chemicals or toxic materials known to have contained arsenic.

Clinical Features

The clinical features of arsenical poisoning are well known. In acute poisoning nausea, vomiting and diarrhea occur suddenly. In severe cases, these manifestations may be followed shortly by collapse or death. In a few days or weeks hyperkeratotic skin lesions usually develop, along with evidence of peripheral neuropathy and changes in fingernails. In patients with chronic exposure, acute gastrointestinal symptoms may be absent, and the first signs are those of nervous-system involvement or nonspecific manifestations such as weakness, prostration, muscular aching and personality changes.

Onset

The onset of the illness in our 41 patients was generally of three types. In the largest group, consisting of 31 patients, the onset was sudden and often dramatic, with the development of acute nausea, vomiting and diarrhea.

A second group of 7 patients had a gradual onset, with development of sensory disturbances in the extremities. Although a history of nausea and vomiting could sometimes be obtained in these cases by direct questioning, these symptoms either were very mild or had preceded the neurologic manifestations by several weeks and were not considered by the patient as part of his illness.

In 3 cases the exact time of onset of the illness could not be definitely determined. These patients complained of fever, respiratory symptoms, abdominal pain and chronic prostration, and of symptoms involving practically every system in the body. The diagnosis in such cases was difficult. There was no known exposure to arsenic, and the manifestations of gastroenteritis and peripheral neuropathy were overshadowed by the systemic symptoms.

Gastrointestinal Manifestations

The acute symptoms of nausea, vomiting and diarrhea appeared immediately after exposure to arsenic. They usually subsided within a few days but occasionally remained for several weeks. The majority of patients did not associate these symptoms with exposure to arsenic and were thought by their physicians to have nonspecific gastroenteritis. An occasional patient complained of dysphagia because of burning of the mouth and throat. Abdominal pain was often severe but was not always present. Small amounts of blood occasionally appeared in the vomitus, but blood was rarely noted in the stools. Very few of the patients were seen at this hospital at the time of their gastrointestinal symptoms, and hence little is known regarding the physical signs of this stage of the illness.

Lesions of Skin and Mucous Membranes

Cutaneous manifestations of arsenical intoxication were noted in 21 of our patients and corresponded to those described by Kelynack.[3] The lesions usually appeared one to six weeks after the onset of the illness. In most cases a diffuse, branny desquamation developed over the trunk and extremities. This was usually described as dry, scaling and nonpruritic. Large portions of the skin over the trunk and arms were often dark and deeply pigmented, suggesting the possibility of Addison's disease. Hyperkeratotic scaling areas, particularly over the palms and soles, were a prominent feature. Herpetic lesions about the mouth were sometimes noted. There was no evidence of the acute erythematous reaction, with subsequent weeping and exfoliation, characteristic of dermatitis caused by hypersensitivity to organic arsenical compounds.

Soft pitting edema was present in 14 patients. This appeared within a week of the onset of the neuritis and was usually confined to the feet and legs. Occasionally, it became generalized, involving the face, trunk and arms.

Irritation of the mucous membranes was a frequent symptom. This consisted of mild conjunctivitis with lacrimation and photophobia, rhinitis with nasal congestion or an irritating cough. Sore throat and burning sensations in the mouth and tongue were also mentioned. One patient had stridor caused by edema of the soft palate and uvula.

Eleven patients had systemic manifestations of respiratory infection, with severe cough, fever, sweats and malaise. Two of them had evidence of pneumonia, with rales, hemoptysis and chest pain. Signs of bronchopneumonia and atelectasis were also present on x-ray examination.

FIGURE 1. *Typical Transverse White Striae in the Fingernails (Mees's Lines) Two and a Half Months after the Onset of Acute Gastrointestinal Manifestations of Arsenical Poisoning.*

Feverishness and drenching sweats, without localizing symptoms, were reported as prominent symptoms early in the illness of 5 patients.

FINGERNAIL CHANGES

Transverse white striae (Mees's lines) were noted in the fingernails in 21 patients, all of whom had had symptoms of arsenical intoxication for six weeks or more. Approximately thirty or forty days are required for these lines to appear above the lunulae, and for this reason they were presumably not detected in the 4 patients observed for less than that time. In many of the other patients no mention was made in the hospital records of either the presence or the absence of the lines, and we cannot be certain whether the nails were thoroughly inspected.

An approximate estimation of the time of the exposure to arsenic could be made in most patients by consideration of the distance of the line from the base of the nail. There was no evidence that fingernail growth was retarded in these patients by arsenical neuropathy. In 1 patient migration of the lines to the free edge of the nail was found five months after exposure. This is approximately the time required for the nail to grow from the matrix to the free edge in normal persons.[12]

The characteristic Mees lines (Fig. 1) appear as single, solid, transverse white bands about 1 or 2 mm. in width completely crossing the nail and appearing in all fingers at the same relative distance from the base.[13] A characteristic amber color bordering the white striae has also been noted by one of our staff members (Dr. Jack Myers). An occasional patient had double white lines several millimeters apart, possibly indicating several exposures to arsenic. In 2 patients, the lines involved the nails of both fingers and toes. None of our patients showed the characteristic transverse furrows of Beau's lines, which are known to follow a variety of acute debilitating illnesses.

Our interest in fingernail striae has led us to observe transverse white lines in 5 patients with illnesses other than arsenical intoxication and without a history of exposure to arsenic. In 2 of them, analyses of both hair and urine failed to reveal the presence of arsenic, indicating that the bands are not pathognomonic of arsenical ingestion. A third patient, who had recurrent pneumonia, showed 0.3 mg. of arsenic per 100 gm. of hair but had no history to suggest arsenical poisoning. Determinations of excretion were not made in the remaining 2 patients, who had bronchogenic carcinoma and carcinoma of the stomach respectively.

NEUROLOGIC MANIFESTATIONS

General

Headache, poor memory and drowsiness bordering on stupor were major symptoms in 7 cases. These patients also had transient episodes of confusion, with irrational speech and delirium. These cerebral manifestations, however, were considerably less severe than those observed in the fulminating, rapidly fatal type of hemorrhagic encephalopathy that occasionally occurs with arsphenamine intoxication. Only 1 patient had generalized convulsive seizures at the onset of the illness. Dimness of vision or diplopia was mentioned occasionally. Evidence of optic neuritis was found on admission in a patient who had had transient blindness lasting several days early in the course of the illness. No other cranial-nerve abnormalities were observed. Disturbances in bladder function, with retention incontinence and frequency, were noted in 4 patients, 2 of whom required indwelling catheters.

Peripheral Neuropathy

In most cases symptoms of peripheral neuropathy were noted one to three weeks after the presumptive exposure. The onset was characterized by the appearance of numbness, tingling and sensations of "pins

and needles" in the feet and later in the hands. Although several patients complained of "burning" sensations, severe sharp or shooting pains were not as prominent as the usual textbook description indicates. Muscle cramps were occasionally noted. Within a few days of the onset of sensory symptoms, weakness developed in the feet and legs. This usually became severe and was generally the presenting complaint.

Sensory examination revealed a decrease in touch, pain and temperature sensations in the hands, feet and lower legs in a symmetrical "stocking-glove" distribution. In mild or early cases impairment of vibratory sensations in the feet was the only evidence of sensory disturbance. In patients with severe damage, loss of vibratory and position sensations in the feet was a frequent occurrence and resulted in ataxia and inco-ordination. Pseudoathetosis also appeared in advanced cases. Dysesthesias and tenderness of the calf muscles were also noted.

The appearance of severe symmetrical muscular weakness of the extremities was an outstanding feature. This was predominantly distal but sometimes involved the more proximal muscles and rarely the shoulder and pelvic girdles. Twenty-seven patients had evidence of foot drop, 24 were unable to walk, and 16 were unable to stand without assistance. Severe weakness of grip and wrist drop was found in 21. The tendon reflexes were generally absent or diminished at the ankle, knee, wrist and elbow. In the most seriously ill patients all tendon reflexes were absent. Atrophy of the muscles of the legs below the knee and of the small muscles of the hand developed rapidly and was proportionate to the severity of the intoxication. Fasciculations were observed in a few cases.

Laboratory Findings

Abnormalities in the peripheral blood were occasionally found. Six patients had a normochromic anemia, with hemoglobin values ranging from 9.5 to 11.8 gm. per 100 ml. Peripheral white-cell counts were also low, ranging from 2900 to 4300 in 8 patients, 3 of whom had neutropenia. Anemia and leukopenia were frequently found in the same patient, but the leukopenia disappeared within three weeks. Eosinophilia (counts of 5 to 14 per cent) was present in 11 cases, in 6 of which obvious dermatitis was observed.

Urinalyses and blood nonprotein nitrogen determinations were negative except in 2 of the cases with fatal outcome. These patients had proteinuria, white blood cells in the urinary sediment and elevation of nonprotein nitrogen levels to 78 and 103 mg. per 100 ml. Determinations of urinary lead excretion were made in 6 cases and were negative in all.

Liver-function tests were performed in approximately a third of the patients and showed only mild abnormalities in cephalin flocculation and thymol turbidity in 4.

The spinal fluid was examined in 28 patients, all of whom had cell counts within normal limits. Five patients had spinal-fluid protein levels between 51 and 60 mg., and 3 others levels of 75, 120 and 265 mg. per 100 ml. The colloidal gold showed mild abnormalities in the first and second zone in 3 cases.

Seven patients had electroencephalograms taken, all being within normal limits except 1, which showed diffuse slow-wave abnormalities.

Electrocardiograms in 21 patients revealed no constant features. Approximately half were normal, the remainder showing various changes such as sinoatrial tachycardia, left-axis deviation, nonspecific T-wave changes and occasional ventricular extrasystoles.

Arsenical Levels in Tissues and Urine

High levels of arsenic were found in either the urine or the hair in all the patients in this study except for 1 in whom analyses for arsenic were not carried out. This patient had accidentally ingested Paris green, and characteristic clinical findings developed within a few days. In 33 patients the concentration of arsenic in a twenty-four-hour specimen of urine ranged from 0.1 to 6 mg., with a mean of 0.9 mg. Only single samples of urine could be obtained in 2 patients. The content in these samples was found to be 0.02 and 0.03 mg. The diagnosis in the remaining 5 cases was based on levels of arsenic in the hair varying from 2 to 5 mg. per 100 gm. of hair.

In general the concentration of arsenic in the urine varied inversely with the duration of the illness. In the 7 patients with urinary levels of 0.8 mg. or more the duration of the neuritis was less than four to six weeks. Most of the patients had neuropathy of four to eight weeks' duration and showed twenty-four-hour urinary excretions ranging from 0.1 to 0.4 mg. One patient had a level of 0.4 mg. of arsenic as long as ten months after onset of neuropathy, but the possibility of continuous exposure to arsenic during this period could not be excluded.

Twelve patients had an analysis of hair for arsenic. The levels usually ranged from 2 to 8 mg. per 100 gm. of hair, but 1 patient had as much as 16.6 mg. eight weeks after his illness. Although some of the patients with high urinary levels also had high hair content, no correlation could otherwise be made between the two determinations. No attempt was made to determine which portion of the hair showed the highest amounts of arsenic nor to compare the arsenical levels of hair taken from various portions of the body. Fingernail parings in 2 cases showed levels of 3.2 and 8.0 mg. per 100 gm. of nail.

The immediate effects of BAL (2,3, dimercaptopropanol) therapy on the urinary excretion of arsenic was observed in 3 patients. In 2 of them, there was no significant increase in excretion after treatment (Fig. 2). One patient had been exposed to arsenic a month previously and had a high urinary level, which fell precipitously before therapy, whereas

the other had neuropathy for four months and showed little change in his low level of excretion during the period of observation. The third patient had several exposures to lead arsenate, the last contact being two weeks before admission. His twenty-four-hour urinary excretion was 6 mg. — a value more than twice that of any other patient in this study; analysis of the

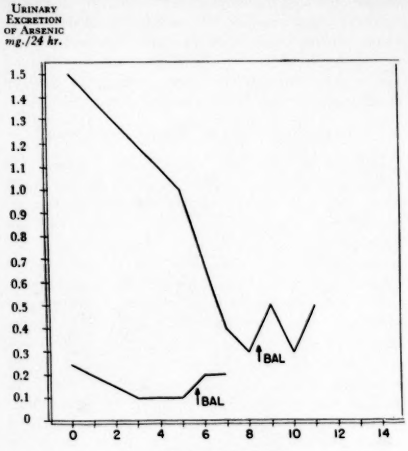

FIGURE 2. *Twenty-four-Hour Urinary Excretion of Arsenic before and Immediately after the Beginning of BAL Therapy.*

twenty-four-hour sample of urine a day after BAL therapy was begun revealed an increase in excretion to 10.4 mg.

The rate of decline of arsenic in the urine was observed in 10 patients who had analyses of twenty-four-hour samples two to sixteen weeks after BAL therapy was begun (Fig. 3). In general the patients with high levels showed a marked decrease in excretion two to four weeks after BAL, and those with smaller quantities showed a more gradual decline in their rate of excretion. The excretion in these patients seemed to differ little from that observed in the patients who had repeated arsenical studies without BAL therapy.

Differential Diagnosis

The neurologic findings of arsenical neuropathy are not characteristic and cannot be distinguished from those in a wide variety of toxic, metabolic and degenerative neuropathies. Although differential diagnosis of intoxication with arsenic may involve a great number of conditions, from a practical standpoint relatively few types of neuropathies have been difficult to differentiate.

In this hospital many of the patients with arsenical neuropathy were initially thought to have Guillain–Barré disease (infectious neuronitis). The differentiation of the two conditions is usually relatively simple since arsenical neuropathy rarely produces cranial-nerve lesions and is associated with more prominent sensory manifestations and more severe weakness of the distal portions of the extremities. Differentiation can almost always be made on the basis of the spinal-fluid findings since only a few patients with arsenical poisoning had spinal-fluid protein levels above 60 mg. per 100 ml.

Alcoholic or nutritional polyneuropathy presented the greatest difficulty in diagnosis, particularly since arsenical intoxication was frequently associated with an alcoholic debauch. Patients with this type of nutritional neuropathy often have other evidence of chronic alcoholism such as Wernicke–Korsakoff syndrome, cirrhosis of the liver or delirium tremens. Arsenical intoxication usually produces a more rapid

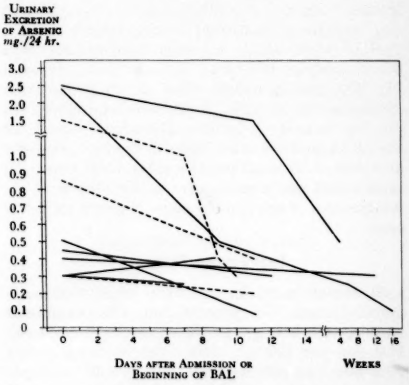

FIGURE 3. *Twenty-four-Hour Urinary Excretion of Arsenic in Patients with and without BAL (the Dotted Lines Represent Untreated Cases, and the Solid Lines Those Treated with BAL).*

progression of neuropathy, with early severe involvement of the upper extremities.

Diabetic neuropathy should also be mentioned in differential diagnosis since it frequently causes burning, painful sensations in the legs, gastrointestinal disturbances and disorders in bladder function. It rarely involves the hands or upper extremities, and differentiation from arsenical neuropathy is not difficult. The trophic changes seen in diabetes, such as perforating ulcers and arthropathy, are not found in poisoning with arsenic.

Neuropathy associated with acute porphyria may at

times be confused with arsenical poisoning. Both conditions may produce severe abdominal pains, mental symptoms, convulsions and predominantly motor weakness of the extremities. The cranial nerves are often involved in porphyria, however, and cutaneous sensory loss is rare. The diagnosis can usually be made by examination of the urine for the presence of porphobilinogen.

The possibility of arsenical neuropathy should be considered in all patients with symmetrical peripheral-nerve lesions who reside in rural areas where arsenical compounds are used as pesticides. The clinical diagnosis in such cases can be usually made whenever gastroenteritis, hyperkeratotic skin lesions and transverse lines in the fingernails are present.

Therapy and Prognosis

The treatment of arsenical polyneuropathy consisted usually of correction of any nutritional deficiencies present, symptomatic measures for relief of pain and physiotherapy and, since 1948, one or more courses of BAL. In an occasional patient with long-standing neuropathy and low urinary excretion, BAL therapy was omitted, and the treatment consisted primarily of physiotherapy and rehabilitation.

The usual doses of BAL consisted of 2.5 mg. per kilogram of body weight, given intramuscularly every four hours for the first two days and once or twice a day thereafter for nine to fifteen days. In more severe cases, particularly in patients with recent acute exposure to arsenic, larger amounts of BAL were administered for longer periods. Aspirin and sometimes codeine were occasionally necessary for relief of painful, burning sensations. High-calorie diets with vitamin supplements were indicated in patients who had been vomiting and had evidence of malnutrition. Specific vitamins such as B_{12}, liver extracts, cortisone and ACTH therapy were not employed. Intensive physiotherapy was given to all patients and consisted of passive and active exercises, gait retraining and measures to prevent contractures. Braces were applied as indicated to correct foot drop.

Careful follow-up observations have been made on 35 patients. Ten of them were observed for a year or more, 20 for four to eleven months, and only 5 for three months or less. Twenty-two of these patients were treated with BAL; 13 received nonspecific measures only. The two groups were similar in both severity and duration of neuropathy, and in the period of follow-up observation. Recovery of sensory and motor function in both groups was invariably slow, and there was no evidence that the time of onset or extent of improvement was affected by the use of BAL. Moreover, the use of large doses of BAL or administration of a second course of therapy failed to produce any demonstrable differences in the degree of improvement.

The early signs of recovery appeared approximately six weeks after the onset of the neuropathy, but significant changes could not be detected for ten to twelve weeks. Improvement in sensory and motor function was always extremely slow but continued steadily throughout the first year of observation, after which further gains could be ascribed to adaptation to the handicap or more efficient utilization of orthopedic aids.

The degree of recovery usually varied with the severity of the neuropathy. Patients with slight weaknesses in the feet and legs and moderate sensory disturbances generally recovered completely although the Achilles reflex often remained diminished to absent. Patients with complete foot drop and total "stocking" anesthesia (this group comprising the majority of our cases) continued to have moderate weakness of dorsiflexion of the feet and impairment of position and vibration sensations at the end of the observation period. Such patients, however, showed a return of proximal muscle strength and were able to walk long distances, particularly when orthopedic appliances were utilized. Recovery of function was usually better in the upper extremities, strength and sensation returning to practically normal in all cases. An occasional patient with severe involvement of the hands, however, continued to have evidence of weakness of the hands and sensory disturbances, along with difficulty in co-ordination of fine movements. The tendon reflexes in both upper and lower extremities generally returned, particularly those at the more proximal joints. As sensory impairment improved, distressing pains in the extremities sometimes appeared, but these usually subsided within several weeks.

Histologic Changes in Peripheral Nerves and Visceral Organs

Biopsies of the distal portion of the superficial peroneal nerves on the dorsum of the foot were taken in 7 cases, in 2 of which anatomic changes could not be found. The remaining 5 biopsy specimens showed destructive changes consisting of fragmentation and resorption of myelin and disintegration of axis cylinders. Atrophy of the nerve and interstitial fibrosis were present in specimens removed late in the course of the illness. One patient with a history of two exposures to arsenic had evidence of both recent and old damage. In some nerves there was complete degeneration of the axons, resorption of myelin and proliferation of the cells of Schwann, indicative of previous injury. Other nerves showed acute degenerative changes affecting both myelin and axis cylinders. Examination of the brachial plexus, femoral nerves and ulnar nerves in the 3 patients dying of arsenical poisoning resulted in findings similar to those described above and commensurate with the duration and severity of the illness. The central nervous system was normal.

Examination of the visceral organs in these 3 patients showed only minimal fatty degeneration and

cloudy swelling of the liver parenchyma. There was also mucosal hyperemia and hemorrhage in the stomach, with congestion of the kidneys and occasional hyaline casts. Death in 1 patient was caused by an extensive bronchopneumonia. Another patient died with a clinical picture resembling shock, and the third after several convulsions.

Discussion

The peripheral neuropathy associated with arsenical intoxication is thought to be due to an interference with the pyruvate oxidase system by arsenic, the supply of energy to the nerve cell from breakdown of carbohydrates thus being blocked. The inactivation of carbohydrate metabolism at this level probably requires only small amounts of arsenic and can account for the poor correlation observed between the severity of the symptoms of the neuropathy and the level of urinary excretion. The amount of arsenic excreted in the urine of our patients was usually large during the first few weeks after exposure but later fell to low levels, which remained practically constant. The prolonged excretion of arsenic in the urine months after exposure probably represents release of the material from various tissue stores in the body. Whether the extremely slow recovery of neurologic function noted in our patients is related to possible repeated exposure of the nerve cells to the arsenic thus released or whether it represents a slow regeneration of nerve fibers or enzyme systems, or both, has not been established.[8]

The 22 patients in this study treated with BAL failed to show any dramatic improvement or an accelerated recovery of sensory and motor function. Most of them, however, were treated six to eight weeks after exposure to arsenic, when the metal may have been fixed to the tissues and could not be removed with BAL. It is of interest that neither of the 2 cases of this condition reported in the American literature yielded evidence of rapid improvement of the neuropathy after BAL therapy.[14,15] Indeed, 1 patient treated within a month of exposure had an aggravation of neurologic signs and symptoms associated with a slight increase in urinary excretion of arsenic. Adverse effects of BAL therapy, however, were not noted in any of our patients. Although the evidence that BAL increased the excretion of arsenic in these patients has not been demonstrated, we believe that this form of therapy is indicated particularly in patients with recent acute exposure to arsenic. Early treatment may result in an increased excretion and may thus prevent some of the serious complications such as convulsions, mental changes and pneumonia. Whether the subsequent neuropathy will be prevented by early treatment has not been determined.*

*Since this manuscript was submitted for publication, we have observed a patient in whom peripheral neuropathy developed in spite of early and adequate BAL therapy for arsenical poisoning.

The clinical picture of arsenical intoxication as outlined above differs little from that described in the literature and textbooks.[16] We have, however, observed several other neurologic syndromes accompanied by high levels of excretion of arsenic. One such patient with Mees's lines in the fingernails had all the symptoms of Guillain–Barré disease, with respiratory paralysis and high spinal-fluid protein. Another showed the clinical picture of polymyositis. Whether the high excretions of arsenic in these patients were coincidental or whether they were evidence of intoxication is a matter for further study.

A survey of the "normal" excretion of arsenic of the rural population in this area would be of considerable interest. The average farm worker using arsenical compounds seems to take little precaution in handling this material and may well have a seasonal elevation in excretion. Physicians in these areas should be alert for clinical evidence of intoxication in these persons, and undoubtedly many more cases of poisoning will be uncovered. A review of the medical records at the Roper Hospital in Charleston, South Carolina, for the past five years has disclosed 30 patients with arsenical intoxication, approximately half of whom were children.[17] The source of the poisoning in the majority of these cases could not readily be determined. This experience coincides with our own. It seems possible for accidental contamination of food, drinking containers and cooking utensils to occur in homes where arsenical compounds are widely employed as pesticides.

It should be emphasized that neither the signs of the peripheral neuropathy nor the pathologic changes in the peripheral nerves are specific for arsenical intoxication. The diagnosis of this condition therefore depends almost entirely on toxicologic analysis whenever poisoning is suspected.

Summary and Conclusions

The epidemiologic, clinical and laboratory features in 41 patients with arsenical neuropathy are analyzed, and the effects of BAL therapy reviewed. BAL administered seven or more days after arsenical exposure has little effect on the subsequent course of the neuropathy.

We are indebted to Dr. George Margolis for his valuable assistance in the preparation of the histologic data.

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ESOPHAGEAL HIATUS HERNIA*

Repair from Below

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DURING the past ten years, the x-ray diagnosis of esophageal hiatus hernia has been made at the Rhode Island Hospital in approximately 350 cases. In 93, or over 25 per cent, surgical repair has been carried out. My own experience has been with 15 cases by the thoracic and 28 by the abdominal route, totaling 43 cases. The remaining 50 operations were carried out by 11 other surgeons. Operation was recommended only for the relief of symptoms and then only after a reasonable trial of medical therapy. It is now believed that more of these patients should be operated upon since there is a definite tendency for the hernia to become larger, requiring operation at an age when the mortality is higher and when complications are more likely to occur.

Since there has always been some disagreement about the relative merits of the transthoracic and the transabdominal approach, it is of interest that, in this series, 42 operations were done by the former and 51 by the latter method. It is, therefore, tempting to make a comparative study of the results in these two groups of cases. However, because of the many factors involved, it would be of little or no statistical value and is not the purpose of this presentation. It is rather to express my preference for the abdominal route after a reasonable experience with both methods, to give the reasons for this choice and to speak briefly of the technic that has been employed.

The reason for the change to the abdominal approach was not from dissatisfaction with the thoracic operation, but was more or less accidental. In December, 1951, an obese, fifty-one-year-old woman presented herself with a large incisional hernia that had followed a cholecystectomy. She was also having symptoms from a large hiatus hernia. A transabdominal operation was carried out, and both lesions were repaired. This operation proceeded so smoothly and the convalescence was so benign that it was decided to try this method in subsequent cases. To date, 51 transabdominal operations have been performed.

The fact that there have been 5 recurrences in operations from above and so far only 1 from below (in a seven-month-old infant with complete obstruction at the esophagogastric junction) is not offered as an argument for the latter method, but is attributed to early inexperience and the belief that an inadequate repair was carried out in these cases. In my opinion, the actual approach to the site of weakness has little or nothing to do with recurrence, and, in experienced hands, a good result should be expected with either method. The preference for the abdominal route is for other reasons. These may be briefly stated as follows:

In the experience at the Rhode Island Hospital the poor-risk patient tolerates a relatively short incision of the upper abdomen better than the thoracic operation. In the former, the patient lies on his back in a relaxed position with both pleural cavities undisturbed, whereas in the latter, he must lie on the right side with the left pleural cavity open and the left lung partially collapsed and with an incision made through the diaphragm to obtain adequate exposure of the crura. In the abdominal series, there were 5 patients with moderately severe heart disease, 3 with obesity (weight of over 220 pounds), 1 with arthritis who had been bed ridden for twenty-five years and was operated on for repeated hemorrhages and 4 in their eightieth year. One elderly poor-risk patient was operated on for the third time after two previous repairs carried out in another city. In my opinion, a transthoracic operation in many of these cases would not have been successful.

Although, in the patient who is a good risk, convalescence from any thoracic operation is reasonably benign and without complications, the fact remains that chest-wall pain is at times quite

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troublesome. Convalescence from the abdominal operation is comparable to that of a cholecystectomy.

Harrington[1] has referred to esophageal hiatus hernia as "the masquerader of the upper abdomen" because it tends to mimic many other conditions. This has been my experience, and when confronted with multiple disease, especially cholecystitis and peptic ulcer, I have frequently found it impossible to be certain of curing the patient with a single operation. For instance, in the 51 abdominal cases, 8 patients had had cholecystectomy without relief of symptoms. One patient, who had had a transthoracic repair of a hiatus hernia in another city, required a subtotal gastrectomy two years later for recurrent bleeding from a duodenal ulcer that had been present at the time of the first operation.

TABLE 1. *Age Groups.*

AGE	PATIENTS WITH THORACIC OPERATIONS	PATIENTS WITH ABDOMINAL OPERATIONS
7 mo.	—	1
20-29 yr.	1	—
30-39 yr.	1	—
40-49 yr.	4	4
50-59 yr.	18	16
60-69 yr.	12	22
70-79 yr.	6	8
Totals	42	51

Since many of these patients are in the middle or older age groups (Table 1) and are suffering from abdominal symptoms, it seems obvious that a careful abdominal examination is of definite value. Of the 51 patients operated upon by the transabdominal approach a diseased gall bladder was found and removed in 15. It is a well accepted fact that a certain percentage of patients with gall-bladder disease show a normal filling. In 1 such patient in this series 9 nonopaque stones were discovered at operation. Eighteen operations were carried out for recurrent hemorrhage; 7 of these patients also had duodenal ulcer. A subtotal gastrectomy was also performed in these cases. Other abdominal disease dealt with included leiomyoma in 1 case, ectopic pancreatic mucosal cyst of the stomach in 1 case, diverticulum of the duodenum in 1 case, a large incisional hernia in 1 case and epigastric hernias in 2 cases. Thus, in the 51 operations performed, 28 additional procedures were carried out that would have been impossible if the patients had been operated on by the transthoracic approach (Table 2). It is obvious that a large percentage, although possibly not all these cases, would have had to undergo additional surgery at some future time. There was 1 death in this group, in a poor-risk cardiac patient who was having massive hemorrhage and who had required 3.5 liters of blood before operation. With this exception, there was considered to be no increase in morbidity among the 28 patients who underwent multiple operations.

TABLE 2. *Associated Operations.*

OPERATION	NO. OF CASES
Cholecystectomy	15
Subtotal gastrectomy	7
Repair of epigastric hernia	2
Repair of incisional hernia	1
Repair of duodenal diverticulum	1
Resection of leiomyoma of stomach	1
Resection of ectopic pancreatic mucosal cyst	1
Total	28

The sex distribution in the two groups is shown in Table 3.

TABLE 3. *Distribution of Patients According to Sex.*

APPROACH	MALE PATIENTS	FEMALE PATIENTS
Thoracic	22	20
Abdominal	12	39
Totals	34	59

93

SYMPTOMS

The symptoms of esophageal hiatus hernia have been well described in many articles, and there seems to be no reason to tabulate them in detail here, since in this series of 93 cases, they were comparable to those reported by other authors. It was stated above that this condition tends to mimic many other diseases such as cholecystitis, peptic ulcer, heart disease and esophageal diverticulum. The diagnosis should not be difficult if a careful study of the patient is made, but when one is dealing with multiple lesions, there may be some confusion about which condition is responsible. It is in this situation that the transabdominal operation is most useful and should even be employed by surgeons who prefer the thoracic route as a routine.

In approximately a third of the cases, hemorrhage occurred, and with an occasional exception, this tended to be of the slow-leak type rather than massive hemorrhage resulting in shock, although 8 patients were admitted to the hospital with a hemoglobin of 5 gm. per 100 ml. or less. Peptic ulceration in the herniated stomach was only occasionally demonstrated. Reflux esophagitis was common. Incarceration of the hernia occurred in 3 cases.

TECHNIC

Although I have stated the reasons for preferring the abdominal approach for the repair of esophageal

hiatus hernia, it should be emphasized that the actual correction of the defect can be equally well carried out from above and from below the diaphragm. Many excellent articles have been written concerning the factors responsible for the hernia. These opinions have been widely divergent, and the nature of the repairs recommended has varied with each author's concept of etiology. Although there is general agreement that the enlarged hiatus should be closed to a normal size, other steps are suggested that are considered to be equally important.

Sweet[2] and others have recommended plication of the sac. Allison[3] lays great stress upon the phrenicoesophageal ligament, which Barrett[4] regards as of no importance, recommending restoration of the esophagogastric angle by actual suture of these structures. Moreover, Barrett[4] does not agree with the pinchcock theory for preventing reflux, which he believes is controlled by a flap valve of mucous membrane at the esophagogastric junction allowing no obstruction to downflow but resisting reflux. He also agrees with some authors that the left gastric vessels help anchor the stomach below the diaphragm. Suture of the cardia to the undersurface of the left leaf of the diaphragm has been recommended, as has crushing of the phrenic nerve.

Many of the ideas mentioned above are based upon careful anatomic experiments and deserve consideration. The type of repair that has been employed in the 51 patients operated upon by the transabdominal route is relatively simple, and in spite of the fact that most of the suggestions mentioned have been ignored, the results in this series are considered satisfactory. The technic can be simply outlined (Fig. 1).

In the earlier cases, a long subcostal incision was used, but the midline incision, with removal of the xiphoid, is now preferred. The incision is carried about 5 cm. below the umbilicus. The left triangular ligament of the liver is divided. A large pad is placed over the left lobe and retracted. The stomach is drawn downward, and the peritoneum is opened anteriorly to expose the esophagus, which is mobilized by blunt dissection. A rubber tissue drain is placed around it, and traction applied downward and to the left by the assistant. All redundant peritoneum of the sac is excised. The upper portion of the gastrohepatic ligament is divided, and the esophagogastric junction along the lesser curvature is freed up. A sponge and retractor are placed over the upper portion of the stomach to allow further retraction to the left. The right crus of the diaphragm is now plainly in view; the left can be readily palpated as it crosses over the aorta. This is easily exposed by blunt dissection.

The angle formed by the two crura is closed with a suture of No. 4 silk. Traction on this first suture brings the remaining portions of the crura more plainly into view. The closure is continued, and, as a rule, four or five sutures are placed. Suturing posteriorly should be discontinued when there is any evidence of tension, and the remainder completed anteriorly until the newly formed hiatus barely admits the tip of the finger. The policy has been to place the esophagus about 1 or 2 cm. below the diaphragm and, as a final step, to suture it to the margin of the new opening with No. 1 silk.

Of the 51 patients operated on by this technic, only 1 could be classified as having a short esophagus. In this case the suturing was accomplished at the esophagogastric junction without difficulty. It is believed that leaving the esophagus below the diaphragm may be an important factor in preventing reflux. This tends to allow the esophagus and the cardia to assume their normal anatomic positions. When the closure of the hiatus is made only at the esophagogastric junction, the bell-shaped deformity may be incompletely corrected.

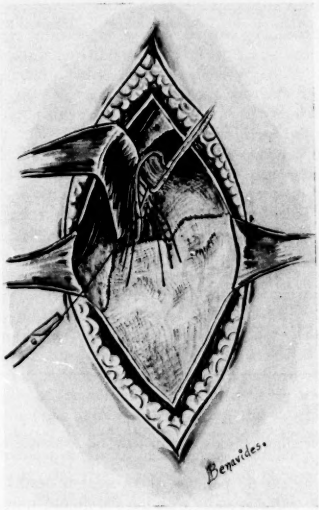

FIGURE 1. *Diagram, Showing Exposure and Suturing of the Crura.*

RESULTS

Among the 93 patients operated upon, there were 5 recurrences in the thoracic group that are attributed chiefly to early inexperience with the operation. The single recurrence in the abdominal group followed an emergency operation on a seven-month-old infant with acute obstruction; this operation was also done during the early years. A secondary repair six months later was successful. It is realized that many of the abdominal operations were recent, and perhaps final judgment should be withheld until there is a longer

period of follow-up study (Table 4). However, in this experience, recurrence tended to appear early and could usually be attributed to an unsatisfactory repair.

Of the 51 patients operated upon by the abdominal approach, 1 had mild and occasional symptoms of reflux, but no recurrence of the hernia. Another had some gastric stasis for two months that was attributed to undue traction on the vagus nerve at operation. Of the 18 operated on for bleeding, 2 have had a mild bleeding episode, again with no evidence of recurrence.

TABLE 4. *Duration of Follow-up Study.*

FOLLOW-UP PERIOD	THORACIC ROUTE* NO. OF CASES	ABDOMINAL ROUTE† NO. OF CASES
yr.		
9 -10	5	—
8 - 9	7	—
7 - 8	4	—
6 - 7	6	1
5 - 6	7	—
4 - 5	9	—
3 - 4	2	4
2 - 3	—	8
1½- 2	—	11
1 - 1½	—	12
½- 1	—	10
½	—	1
Totals	42	51
	93	

*2 deaths.
†4 deaths.

Among the 93 patients, there were 6 deaths — 2 with the thoracic and 4 with the abdominal approach.

FATAL CASES

Thoracic Route

CASE 1. A 60-year-old man who had Marie–Strümpell disease, with severe flexion deformity of the spine, for over 35 years and symptoms of obstruction and bleeding for 5 years, was admitted to the hospital during a severe bleeding episode. He required 2500 ml. of blood before operation. Death on the 3d postoperative day was due to pulmonary complications.

CASE 2. A 60-year-old man who had chronic alcoholism died of cardiac arrest during the course of operation. A previous repair had been carried out in another city 5 years before.

Abdominal Route

CASE 1. A 61-year-old woman who was having an uneventful convalescence died suddenly on the 10th postoperative day of a pulmonary embolism.

CASE 2. A 58-year-old, obese woman with a low pulmonary reserve who had had 3 previous admissions to the hospital because of hemorrhage was admitted with a hemoglobin of 5 gm. per 100 ml. She was kept on the medical service for 6 weeks to improve her general condition. She withstood the operation quite well, but postoperatively pulmonary complications, with considerable coughing, developed, resulting in wound disruption. This combination of events caused the patient's death on the 7th postoperative day.

CASE 3. A 65-year-old man who was considered to have severe cardiac disease was admitted to the hospital with massive hemorrhage and given 3.5 liters of blood before operation. X-ray examination showed a large hiatus hernia and a chronic duodenal ulcer. The surgeon elected to repair both lesions, and although the patient lived for 15 days, his convalescence was stormy and death was attributed to cardiac failure. (A high mortality is to be expected in this type of case, and it is possible that a subtotal gastrectomy or suture of the duodenal ulcer alone should have been carried out.)

CASE 4. A 75-year-old woman was admitted to the hospital with an incarcerated hiatus hernia. She had coronary-artery disease, and although the operation was well tolerated and she was up and about, she died suddenly of a coronary infarction on the 3d postoperative day.

Although 6 deaths in a series of 93 cases may be considered to constitute a high mortality figure, mortality, as always, depends mainly upon the selection of cases. It is of interest that 4 patients in their eightieth year had a benign and uncomplicated convalescence. Some may question the wisdom of operating on some of these elderly, poor-risk patients. However, the serious nature of their symptoms, which, in this group, were for the most part intolerable or of an emergency nature, was considered. Two deaths occurred in patients with massive hemorrhage. One is frequently faced with the same problem in the elderly patient who is bleeding severely from peptic ulcer. The high mortality in this group is well known. Sudden death from coronary infarction and pulmonary embolism will continue to occur occasionally in spite of all precautions that may be taken in a group of patients of this type.

SUMMARY AND CONCLUSIONS

Experience with operations upon 93 patients with esophageal hiatus hernia is reviewed. Although a satisfactory repair can be carried out from either above or below the diaphragm, the latter route is favored since in this series the technic was simpler and was better tolerated by the poor-risk patient. In addition, this approach allows for the correction of other intra-abdominal disease and permits a careful exploration of the peritoneal cavity.

I am indebted to Miss Louise Wicks for her assistance in abstracting the case records and to Dr. Jorge Benavides for the diagram illustrating the technic.

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THE TEMPORARY THROMBOTIC STATE*

Application of This Concept to the Therapy of Recurrent Thromboembolism, with Bacteriologic and Roentgenologic Considerations in the Differential Diagnosis of Pulmonary Infarction and Pneumonia

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NOT infrequently the physician is confronted with a patient in whom massive recurrent pulmonary infarction occurs without an evident source for emboli or a recognized cause for local thrombosis. The management of this syndrome and its differentiation from other conditions, particularly pneumonia, is made difficult by the lack of a reliable clinical or laboratory test for the incipient or actively thrombotic state. It is the purpose of this report to present a concept — "the temporary thrombotic state" — that has proved helpful in the treatment of recurrent thromboembolism and pulmonary infarction; secondly, to summarize briefly the important diagnostic clinical, bacteriologic and roentgenologic features distinguishing pulmonary infarction from pneumonia; and, finally, to illustrate the value of these observations in the successful management of a patient with recurrent pulmonary infarction of unknown origin.

"THE TEMPORARY THROMBOTIC STATE"

Recurrent attacks of deep venous thrombosis and pulmonary embolism in otherwise healthy young people are not rare. Repeated bouts may develop, and then, without further therapy and for unknown reasons, they disappear and may never recur. These thromboembolic episodes, though usually benign, may terminate in sudden death or result in chronic cor pulmonale or severe peripheral venous insufficiency. Yet the nature of the clotting derangement in these patients has not been elucidated.

Since the time of Virchow intimal damage, stasis and increased coagulability of the blood have been postulated as the principal mechanisms whereby thrombus formation may be induced. In the past most of the emphasis has been placed on the first two of this triad. In the light of recent advances in knowledge of the clotting mechanism, however, the role of hypercoagulability in the initiation of intravascular coagulation deserves rescrutiny.

Recently, it has been demonstrated that intravascular thrombi can be induced regularly in dogs by the systemic infusion of normal heterologous canine serum or fractions thereof.[1] The serum induces a hypercoagulable state lasting several minutes, during which massive venous thrombosis develops *in veins containing stagnant blood far removed from the site of infusion*. Under the same conditions plasma is inert. The serum or serum fraction effective in producing this reaction is rich in convertin and possibly some other as yet uncharacterized moiety. Venous stasis need only be partial, and endothelial injury plays little if any part in the reaction.[2]

The significance of these observations is heightened by the reports of several investigators[3-6] describing a temporary rise in the convertin complex during pregnancy and in the early puerperium — a period in which venous thrombosis and pulmonary embolism are not uncommon. When it is recalled that the pregnant state is associated with significant peripheral venous stagnation and that at delivery an extensive amount of serum is elaborated, the experimental conditions outlined above mimic in these two respects those obtaining in the gravid woman at term. Similarly, the temporary increase in platelet adhesiveness during the postoperative period[7] may be significant in the pathogenesis of thromboembolism, which not infrequently complicates major surgical procedures.

Despite these demonstrated alterations in known clotting factors in disorders frequently associated with thromboembolic phenomena, data demonstrating an intimate clinical relation between such alterations and intravascular thrombosis are conspicuously lacking. The crucial obstacle to the verification of such a correlation is the frequent occurrence of extensive intravascular clotting, as demonstrated at autopsy, in the absence of clinical or laboratory evidence of thrombosis.

It has been suggested that the pathogenesis of venous thrombosis in certain clinical conditions may be referable to local venous stasis combined with a transient increase in convertin activity or in some other entity produced during coagulation and present in serum.[2] The amount of clot-promoting activity in serum required for the initiation of experimental intravascular coagulation in dogs is small: during or

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after serum infusion, no detectable increase in convertin activity or any other known clotting factor can be demonstrated at the site of intravascular thrombosis. Failure to demonstrate an abnormality in the coagulation mechanism when clinical thrombosis is evident may therefore merely reflect the inadequacy of current methods for measuring known clotting constituents.

The foregoing clinical and experimental observations have suggested to us a concept that we have termed "the temporary thrombotic state." In the first place, patients with idiopathic intravascular clotting have a hypercoagulable state that predisposes them to thrombosis. Hypercoagulability may be due to either known or as yet undefined alterations in one or more specific clotting constituents. These may include alterations in the convertin complex, platelet adhesiveness and the liberation of thromboplastic elements from gravid uteri, traumatized tissues or necrotic tumors. Secondly, during this abnormal state, the laying down of clot can be initiated and then potentiated by a degree of stasis that would not *by itself* result in thrombus formation. Finally, among these patients with idiopathic intravascular clotting, hypercoagulability and vascular stasis may be systemic or local, transient or prolonged or recurrent.

Much work will be required before this concept can be fully validated. Our studies, for instance, indicate that present methods may be inadequate to detect, biochemically, alterations in coagulability readily demonstrable biologically. The concept of such an abnormal dynamic state — whatever its ultimate fate — provides, however, a fresh and workable basis for the practical management of many difficult problems in thromboembolic disease. Treatment thus becomes predicated, first, upon the effective neutralization of hypercoagulability by the proper use of anticoagulant drugs such as heparin and Dicumarol and, second, upon the reduction of venous stasis through the avoidance of immobilization and through the use of elastic supports. This therapeutic regimen must be invoked in some patients for days, in many for weeks and in a few for months or longer. Failures can often be related to premature curtailment of active treatment.

Pulmonary Infarction versus Pneumonia

Vital to effective clinical management in accordance with the concept outlined above is the ability to diagnose thromboembolism. Diagnosis is currently based largely upon a high index of suspicion, a carefully taken history and a meticulous physical examination. In the absence of a specific test for intravascular clotting, however, all diagnostic measures establishing the presence of thromboembolism or eliminating clinical conditions that simulate thromboembolism should be used to the fullest extent.

A particularly common and difficult diagnostic problem is the distinction between pulmonary infarction and pneumonia. An appreciable number of cases still classified as pneumonias are, in all probability, pulmonary infarction secondary to pulmonary-artery obstruction.[8] Common to both conditions are cough, dyspnea, cyanosis, chest pain, bloody sputum, fever, collapse, tachycardia, leukocytosis and even transient jaundice. Chills, high fever, massive consolidation limited to one lobe and a markedly elevated leukocyte count are, however, less common in pulmonary infarction than in the bacterial pneumonias. Although sharp pleuritic pain and frank bloody sputum are relatively uncommon in the "viral" pneumonias, severe chest pain may complicate epidemic pleurodynia.

Bacteriology

Information of differential value may be gained from careful examination of the sputum. In the bacterial pneumonias, it may be rusty or hemorrhagic but will show many polymorphonuclear leukocytes and, if the patient is seen before treatment, many bacteria with the infecting organism predominating. In "viral" pneumonia the sputum will show relatively few cells, which are principally mononuclear round cells. Bacteria will be few and of mixed types. Early in pulmonary infarction the sputum usually contains little beyond a varying amount of blood. Sputum and blood cultures also help differentiate the bacterial pneumonias from pulmonary infarction.

Many pneumonias of nonbacterial etiology may be recognized in retrospect by serologic procedures. Influenza infection may be diagnosed by hemagglutination inhibition tests, and psittacosis, ornithosis or Q fever by complement-fixation tests. Unfortunately, these are not readily available. However, the cold-agglutinin test, which is performed in most hospital laboratories, shows a diagnostic rise in about 70 per cent of patients with primary atypical pneumonia. Certain pulmonary fungous infections, notably histoplasmosis and coccidioidomycosis, may be recognized by direct smear and culture of the sputum and by skin and complement-fixation tests. It must be appreciated, however, that even with full use of these technics a specific etiologic diagnosis will not always be obtained.

Roentgenology

The diagnosis of pulmonary embolism and infarction is often initially suggested by x-ray examination of the chest. Though there is no unanimity concerning the place of roentgenology in the diagnosis of pulmonary embolism, we have found it extremely useful.

Pulmonary embolism often leads to infarct formation. Infarcts occur most commonly in the lower-lung fields, often in the costophrenic angle, and only exceptionally in the upper-lung fields. They are frequently small, rarely involve an entire lobe and may be accompanied by pleural effusion. Most shadows

representing infarcts are reversible, disappearing from the roentgenogram within days to weeks without leaving any visible trace.[9]

The pulmonary infarct has been presented in its idealized form as a cone with its apex oriented toward the hilus and its base resting upon a pleural surface. It can be demonstrated pathologically, however, that the apical portion of the area supplied by the occluded pulmonary artery practically never becomes infarcted. A more accurate picture is that of a truncated cone. Thus, the search on the roentgenogram for a triangular shadow is not founded on the underlying pathologic changes. An infarct may cast a variety of roentgenologic shadows. For the identification of such a pulmonary shadow as an infarct it is necessary to find a projection whereby a semispherical or half-spindle-shaped consolidation is arranged with its flat and longest diameter along any pleural surface: costal, diaphragmatic, mediastinal or interlobar. Although this topographic relation to the pleura is a prerequisite for the diagnosis of infarction, pneumonic consolidation from any cause may also assume this appearance. The roentgenologic evidence of pulmonary infarction, therefore, must be carefully weighed and combined with other features before the diagnosis can be established.

Since infarcts do not develop in all cases of pulmonary embolism, the diagnostic effort must not be limited to the search for infarcts. Fortunately, x-ray examination provides other, though less reliable, signs of pulmonary embolism. The lodgment of clots in the pulmonary arteries produces local and systemic disturbances — consequences that can often be identified roentgenologically. Acute cor pulmonale, congestive heart failure, pulmonary edema, pleural effusion or changes that reflect respiratory inhibition may be observed. Although shallow respiration in pulmonary embolism is well recognized clinically, the diagnostic significance of its x-ray manifestations is not generally appreciated[10]: these include unilateral or bilateral high position and limited excursion of the diaphragm, a shortened distance between the dome of the diaphragm and the horizontal interlobar fissure and atelectasis, often in the form of basal plate atelectasis. Basal atelectasis results from the accumulation of secretions in dependent bronchi. These atelectatic areas have on occasion been mistaken for infarcts, pneumonic consolidation or pleural effusion. We have nevertheless learned to place great reliance upon this roentgenologic sign of respiratory inhibition in the diagnosis of pulmonary emboli.

In rare cases a large clot can be recognized in the major hilar arteries.[11] Occasionally, the mechanical and reflex changes resulting from acute obstruction to pulmonary arterial flow may produce oligemia manifested by increased translucency of one or both lung fields.[12] With repeated embolization pulmonary hypertension, dilatation and increased pulsation of the hilar arteries will appear. Chronic cor pulmonale secondary to recurrent pulmonary emboli is most characteristic in appearance.[13] It is similar to the heart in mitral stenosis but without dilatation of the left atrium. Thus, in the posteroanterior view there is marked bulging of the second curve on the left, dilatation of the pulmonary artery and concavity in the area of the third curve instead of the prominent convexity seen in mitral stenosis. The dilatation of the right ventricle presents itself best in the lateral and oblique views: plump, tumorlike hilar shadows, oligemic lung fields and dilated superior vena cava and azygos vein[14] complete the picture.

The roentgenogram in pulmonary embolism may show classic infarction, respiratory inhibition with basal atelectasis, oligemic lung fields, dilatation of the hilar shadows, pleural effusion or pulmonary edema. These physiologic and pathologic alterations are the result of the complex interplay of various elements. Isolated, most of these manifestations are nonspecific; occurring in various combinations, however, they fall into a pattern very often unmistakably diagnostic of pulmonary embolism.

Electrocardiography

In only a small percentage of patients with pulmonary emboli is the electrocardiogram helpful in establishing the diagnosis. Nevertheless, tracings should be obtained whenever this condition is suspected. The pattern of acute cor pulmonale is the most characteristic of the observed electrocardiographic changes. Its main features are large S deflections in Lead 1, prominent Q and inverted T waves in Lead 3 and, in some cases, inverted T waves in the precordial leads. In addition there is marked clockwise rotation of the heart, with displacement of the transitional zone to the left, and tall R waves in the right and prominent S waves in the left precordial leads. The sudden appearance, rapid evolution and prompt reversion to normal of these abnormalities distinguish these tracings and help to differentiate them from those of posterior myocardial infarction. Moreover, in pulmonary embolism the QRS complex in Lead aVF is almost invariably normal whereas in posterior myocardial infarction an abnormal Q wave in Lead aVF is usually present.[15] Other electrocardiographic changes encountered in patients with pulmonary emboli are sudden, transient, incomplete right-bundle-branch block and temporary inversion of the T waves in the right-sided precordial leads. These abnormalities are not, per se, pathognomonic of pulmonary embolism and are observed in other conditions. The electrocardiogram is most valuable in substantiating the diagnosis of pulmonary embolism when the electrocardiographic changes are correlated with the remainder of the clinical picture.

Even after the application of all available methods the differentiation of pulmonary infarction and pneumonia remains obscure in some cases. Early differentiation is nevertheless extremely important. The

hazards of delaying treatment for pulmonary infarction are at least as great as the danger of withholding specific chemotherapy in pneumonia, for sudden death or sustained pulmonary hypertension and irreversible cor pulmonale may result from repeated and progressive encroachment upon the pulmonary arterial bed by intravascular clots.[16,17] Indeed, when, in the occasional patient, the diagnostic dilemma cannot be resolved, it appears more prudent to give treatment promptly for both conditions rather than to follow the custom of administering antibiotics and awaiting the patient's clinical response. In our opinion the danger of withholding anticoagulants far outweighs the risk of administration.

Case Report

A 26-year-old accountant (B.I.H. M 48045) was admitted to the Beth Israel Hospital on December 31, 1953, because of "pneumonia" resistant to antibiotic therapy.

He had been in excellent health until 1 month previously, when he noted the sudden onset of a sharp pain in the lower left anterior aspect of the chest that was aggravated by respiration and coughing, and associated with hemoptysis and a maximum temperature of 103°F. The white-cell count was 13,000, with 3 per cent eosinophils. Roentgenograms of the chest showed a consolidation at the left-lung base; a diagnosis of "viral" pneumonia was made, and treatment with oxytetracycline was instituted. The symptoms subsided within 1 week, and the patient was ready to return to work when he again experienced pain in the left side of the chest, as well as hemoptysis and fever. He was admitted to another hospital, where he received penicillin and oxytetracycline and the fever subsided again after several days. At this time the white-cell count was 12,000, with 7 per cent eosinophils. Therapy was stopped because of severe, widespread urticaria, but several days later cough, hemoptysis, fever and right-sided chest pain again recurred. Erythromycin therapy was followed by slight clinical improvement and subsidence of fever. After discharge from the hospital and while at home, the patient experienced general malaise and a slight evening fever (maximum temperature of 100.5°F.). During the month before entry he had lost 25 pounds in weight. X-ray study of the chest during this 30-day period had revealed migratory areas of pulmonary consolidation. Because of the persistence of symptoms and the changing roentgenologic findings, he was admitted to the Beth Israel Hospital. The past history, family history and review of the systems were all noncontributory.

Physical examination showed several urticarial lesions over the right lower and left upper portions of the thorax posteriorly. The anteroposterior diameter of the chest was normal. There was limited expansion of the right thoracic cage, with dullness, decreased fremitus, decreased breath sounds and egophony at the right base. No friction rub was audible. The heart size was normal; the rhythm was regular, and the pulmonic 2d sound was accentuated. There were no murmurs or thrills. The liver, spleen and kidneys were not palpable; there was no abdominal or costovertebral-angle tenderness. All the peripheral pulses were bounding; varicose veins were neither visible nor palpable, and there was no cyanosis, clubbing, edema or calf tenderness. Homans's sign was negative. Neurologic examination was within normal limits.

The temperature was 100.6°F., the pulse 80, and the respirations 25. The blood pressure was 114/72.

The specific gravity of the urine was 1.025; the urinary sediment was normal. Several specimens were free of albumin, sugar, acetone and bile. The hemoglobin varied between 14.1 and 16 gm. per 100 ml., with a hematocrit ranging from 46 to 52 per cent. The white-cell count was 9000, with 74 per cent neutrophils, 12 per cent lymphocytes, 7 per cent monocytes and 7 per cent eosinophils. This differential count was similar on each of 7 examinations except for 1 blood smear on the 6th hospital day that showed 17 per cent eosinophils. The platelet count was 267,000. The bleeding time was 3 minutes, and the clotting time[18] 12 minutes. The prothrombin,[19] accelerator globulin,[20] convertin[21] and prothrombin consumption[22] were all within normal limits before anticoagulant therapy. Capillary fragility was normal. An L.E. preparation of the peripheral blood was normal. Stool examinations on 2 occasions were negative for occult blood, ova and parasites. Repeated sputum cultures were negative for respiratory pathogens, and culture of pleural fluid revealed no organisms. A gram stain of the sputum showed no eosinophils. Pleural fluid obtained on the 2d hospital day contained a protein of 3.9 gm. per 100 ml. and had a red-cell count of 60,000 and a white-cell count of 20,000 with 15 per cent neutrophils, 35 per cent eosinophils, 23 per cent lymphocytes and 27 per cent epithelial cells. The vital capacity was 3.8 liters. The total plasma protein was 6.7 gm. per 100 ml. with 3.2 gm. of albumin and 3.5 gm. of globulin. A 12-lead electrocardiogram on the 4th hospital day was entirely within normal limits. A vectorcardiogram (occasionally helpful in establishing a diagnosis of pulmonary embolism[23]) was also normal.

After the clinical course and a series of roentgenograms of the chest (Fig. 1) had been reviewed a diagnosis of recurrent pulmonary-artery occlusion with infarct formation was made, and intermittent intravenous heparin therapy by indwelling polyethylene catheter[24] was begun on the 3d hospital day. Because of dramatic clearing of the pulmonary disease clinically and roentgenologically, heparin was gradually discontinued over a 24-hour period on the 19th hospital day. On the following morning the patient suddenly experienced right-sided pleuritic pain, hemoptysis, fever and tachycardia. Physical examination revealed decreased breath sounds over the left-lower-lung field and small areas of hyper-resonance at the left base. A roentgenogram of the chest gave new evidence of consolidation on the right and probably additional consolidation on the left, with reappearance of an effusion in the left pleural cavity. Heparin was therefore reinstituted, followed by a gradual subsidence of pulmonary signs and symptoms. On the 30th hospital day while the patient was still on heparin, Dicumarol was started. Heparin was discontinued on the 37th hospital day, when prothrombic activity[25] had been reduced to 10 per cent of normal. During the remainder of the hospital stay he was asymptomatic, and the signs in the chest, as well as the roentgenograms, were consistent with his excellent clinical condition.

On the 43d hospital day he returned home and continued to receive Dicumarol for 3 months. The prothrombic activity was maintained between 5 and 15 per cent of normal during this interval. Two months after leaving the hospital, he returned to work. He has returned periodically to the Beth Israel Hospital for re-evaluation. When seen in January, 1955, he was entirely well and fully active. Urinalysis, blood counts, an electrocardiogram, a vectorcardiogram, x-ray examination of the chest and serum convertin levels were all within normal limits. In October his health was excellent.

Discussion

The diagnosis of recurrent pulmonary infarction on admission was based on the clinical and roentgenologic findings: recurrent migratory pleuritic chest pain, cough, hemoptysis, fever and negative bacteriologic studies accompanied by multiple fleeting pulmonary consolidations and pleural effusions. In accordance with this diagnosis were the subsequent clinical course and the response to anticoagulant therapy. In retrospect, hardly any entity but pulmonary infarction would have been consistent with the clinical findings. Yet each clinical episode and roentgenogram during the month before entry were entirely compatible with a diagnosis of respiratory infection. Only after serial roentgenograms were reviewed and the clinical course evolved, with relapses and

remissions unrelated to antibiotic therapy, did the true nature of the illness become clear. The careful bacteriologic studies of the blood, sputum and bowel represented an important ancillary guide to the correct diagnosis.

blood in the pleural cavity[26] or from pulmonary embolism per se,[27] it was in all probability, in this patient, a manifestation of the hypersensitivity reaction to antibiotic therapy. The possibility of Löffler's syndrome was considered. In Löffler's syndrome,

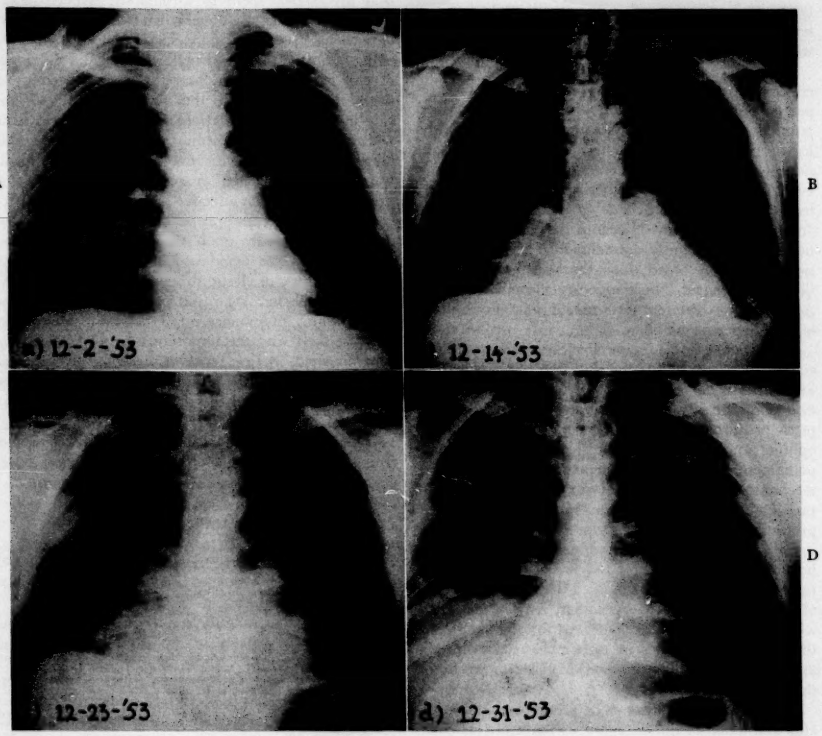

FIGURE 1. *Roentgenograms of the Chest, Showing Multiple Infarcts, Hilar Arterial Dilatation, Respiratory Inhibition and Pleural Effusions before Anticoagulant Therapy.*

A, *taken on December 2, 1953, shows a small, round, ill defined area of consolidation in each lower-lung field, not in obvious contact with the pleura on the available roentgenograms. The left costophrenic angle is obscured by a "hump-shaped" consolidation (infarct). Both leaves of the diaphragm are elevated. The hilar shadows are increased.*

B, *taken on December 14, shows that the right cardiophrenic angle is obscured. There is a small pleural effusion on the left.*

C, *taken on December 23, shows areas of consolidation with pleural contact at the base of the right upper lobe, in the right middle lobe and in the left costophrenic angle (infarcts).*

D, *taken on December 31 (on entry to the Beth Israel Hospital), shows beginning clearing of the consolidation in the right upper lobe, with a pleural effusion on the right; the left base has cleared.*

An unusual feature was the eosinophilia in the peripheral blood and in the pleural fluid. The episodes of pulmonary signs and symptoms were the same at the beginning of the illness when there was no eosinophilia. Eosinophilia appeared concurrently with urticaria. Although eosinophilia may result from

however, the clinical symptoms are mild, and the x-ray findings relatively marked; severe pleuritic pain and hemoptysis are not characteristic.

An unsuccessful search was carried out for clinical conditions commonly associated with thromboembolism. These included congestive heart failure, myo-

cardial infarction, trauma, old or recent venous disease, polycythemia, thrombotic thrombocytopenic purpura, lupus erythematosus, septicemia and multiple myeloma or other malignant tumors. In addition, no abnormalities in known coagulation factors were demonstrated. Similar negative results have been obtained in a number of patients studied in this hospital in whom unexplained and excessive clotting was clinically apparent.

The clinical course clearly indicated that without effective therapy, there was strong likelihood of repeated pulmonary infarction with resultant sustained pulmonary hypertension. No thrombotic focus in the leg or pelvic veins or in the chambers of the right side of the heart was ever uncovered. It could not even be determined whether the pulmonary-artery lesions were embolic or due to localized thrombosis. In the absence of overt venous disease, venous ligation was not seriously considered. Therapeutic considerations were based upon the hypothesis that this illness represented "the temporary thrombotic state." Accordingly, treatment was aimed at neutralization of the hypercoagulability.

No rational guide exists for the choice of anticoagulant agents or for the duration of therapy. An ideal drug is not available at present. There is some evidence that substances such as Dicumarol that depress prothrombin conversion may not provide as optimal an anticoagulant effect as heparinlike compounds that block fibrin deposition through other mechanisms.[28,29] It has been our distinct clinical impression that heparin offers a "broader spectrum" of protection against intravascular clotting than Dicumarol. Intermittent intravenous administration of heparin was continued for two weeks because of experimental evidence that marked decreases in the size of bland pulmonary-artery emboli may be achieved within a week of their lodgment in the lung and that initially nonadherent systemic venous thrombi usually become well organized within two weeks of their formation.[30]

Because of the recurrence of pulmonary infarction after reduction of the dosage of heparin, it was clear that hypercoagulability was still present. The dosage of the drug was therefore again increased, with prompt subsidence of the pulmonary signs. The question was then posed whether this patient should undergo a vena-cava ligation (although no venous thrombosis in the leg or pelvic veins was demonstrable) or whether he should continue to receive anticoagulant therapy for an extended period—perhaps years. Because of the continuing belief that the disturbance in this patient's clotting mechanism was temporary, it was decided to continue with two additional weeks of heparin to be followed by Dicumarol for a period of three months on an ambulatory basis. The seventeen-month follow-up study after discontinuance of anticoagulant therapy appears to have justified the validity of this approach.

Summary and Conclusions

Various experimental and clinical observations have led to a concept that we have termed "the temporary thrombotic state." Patients with idiopathic intravascular clotting have a hypercoagulable state that predisposes them to thrombosis; hypercoagulability may be due to either known or as yet undefined alterations in one or more specific clotting constituents. During this abnormal state the laying down of clot can be initiated and then potentiated by a degree of vascular stasis that would not *by itself* result in thrombus formation. Among these patients with idiopathic intravascular clotting, hypercoagulability and vascular stasis may be systemic or local, transient or prolonged or recurrent. Treatment is predicated first upon effective neutralization of hypercoagulability by the proper use of anticoagulant drugs and secondly upon the reduction of venous stasis through the avoidance of immobilization and through the use of elastic supports.

Clinical, bacteriologic and roentgenologic features distinguishing pulmonary infarction from pneumonia are described, and the importance of x-ray diagnosis is emphasized. A case report is presented to illustrate the usefulness of the concept of "the temporary thrombotic state" and the difficulties in the differentiation of pulmonary infarction from pneumonia.

When pulmonary infarction cannot be distinguished from pneumonia, concomitant antibiotic and anticoagulant therapy should be instituted promptly.

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PSYCHIATRIC DIAGNOSES IN HOSPITALIZED PATIENTS WITH NEUROCIRCULATORY ASTHENIA*

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THE group of symptoms variously known as effort syndrome, neurocirculatory asthenia, Da Costa's syndrome, soldier's heart and so forth, has occasioned considerable comment in the literature. The two features on which most authors agree are decreased exercise tolerance and dyspnea on exertion; other frequent though not universal complaints include palpitation, precordial pain, breathlessness at rest and a host of symptoms such as sighing, syncope, dizziness, anorexia and nervousness. A high familial incidence has been noted.[1,2]

Fundamentally there are three divergent theories concerning this syndrome: that it is based on specific physiologic deficits (a view held chiefly by European investigators)[3]; that it is equivalent to anxiety neurosis[1]; and that it is a frequent accompaniment of various mental disorders — not of anxiety neurosis alone — and in some cases may be predominantly physiologic and in others predominantly psychologic in origin.[4]

The purpose of this study was to ascertain the relation between neurocirculatory asthenia and psychiatric illness in hospitalized patients and, more particularly, to test the hypothesis that it is equivalent to anxiety neurosis. The pertinent physiologic and biochemical findings of other investigators are also reviewed briefly.

METHODS

All patients admitted to the McLean Hospital were routinely seen by one of us and, over a twenty-two-month period from September, 1953, to July, 1955, were carefully examined for evidence of neurocirculatory asthenia. The prime criterion for diagnosis was a history of dyspnea on exertion in the absence of organic disease. Many of the other symptoms referred to above also were present but alone were not considered adequate for the diagnosis. When these patients were discharged, the final psychiatric diagnoses, made independently by the psychiatric staff, were obtained.

During the period under consideration a total of 310 new patients were examined. Of this group 29 had neurocirculatory asthenia, 59 gave no history or a poor history, and 222 who gave an adequate history either showed no dyspnea on exertion or had organic disease to account for this symptom. Of the total number of patients with the syndrome, 3 were still hospitalized at the writing of this report and are not included in Table 1. One patient is included twice, since he had two admissions with different psychiatric diagnoses.

TABLE 1. *Psychiatric Diagnoses of Patients with Neurocirculatory Asthenia.*

DIAGNOSIS	NO. OF CASES
Involutional psychotic reaction	1
Manic-depressive reaction, manic type	2
Manic-depressive reaction, depressive type	1
Schizophrenic reaction, paranoid type	9
Schizophrenic reaction, acute undifferentiated type	2
Schizophrenic reaction, chronic undifferentiated type	1
Schizophrenic reaction, schizoaffective type	3
Paranoid state	1
Psychoneurotic disorder, anxiety reaction	1
Psychoneurotic disorder, depressive reaction	3
Psychoneurotic disorder, schizoid personality	1
Personality disorder, emotionally unstable disturbance	1
Adjustment reaction of adolescence	1

These data strongly favor the concept that neurocirculatory asthenia is a syndrome that occurs in

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many psychiatric disorders and not solely in anxiety neurosis.

Discussion

Reliance on exertional dyspnea as the chief criterion for the diagnosis might be questioned; it may have excluded from Table 1 a few patients who would otherwise have been included. However, the procedure is justifiable on the ground that the other major manifestation — namely, *inability* to undertake strenuous exertion — might be difficult to distinguish in psychotic patients from *unwillingness* to make such effort. It is to be noted that many of the group of 26 had other symptoms of neurocirculatory asthenia: 16 complained of palpitation and 7 of chest pain.

The data of the present study throw no light on the question whether the syndrome occurs more frequently in anxiety neurosis than in psychosis, since most patients with the former do not require hospitalization in an institution such as the McLean Hospital. These data do show that neurocirculatory asthenia is not the equivalent of anxiety neurosis, and they confirm the third of the previously listed theories about the disorder. It is to be noted that even the proponents of the theory that anxiety neurosis and neurocirculatory asthenia are identical are constrained to state that initially hysteria, early schizophrenia, and agitated depression may present difficulty in differential diagnosis.[5]

The mechanism of impaired exercise tolerance has not been established. It is difficult to evaluate research that has been done on a condition whose definition, causes and symptomatology are grounds for dispute; however, the reported physiologic and biochemical studies are in reasonable agreement.

Various cardiorespiratory abnormalities have been described. A failure of pulse rate to diminish normally after exercise is quite constant,[1,6-8] and blood-pressure rise with exercise is excessive.[9] Resting pulse is normal or elevated.[1,9] Rapid, shallow breathing at rest[10] and inefficient ventilation with low oxygen intake during strenuous exercise have been reported.[1] Diminished breath-holding capacity has been observed,[2,11] and low-grade fever, which presumably is due to vasoconstriction caused by sympathetic overactivity, has been noted.[11]

Biochemically, the chief disorder described is an excessive rise of blood lactate and an increased oxygen debt with exercise. When the *same amount of work* is done by both patients with neurocirculatory asthenia and control subjects, the patients show a significantly greater increase in blood lactic-acid concentration and in oxygen debt.[1,6-8] This observation is not in conflict with the fact that on maximal exertion patients stop much earlier and at lower lactate levels than the controls.[1,7] Other experiments have shown that oxygen uptake during exercise is greater in athletes than in untrained men; in turn, this measurement is greater in untrained men than in untrained women, and patients with neurocirculatory asthenia show the lowest exertional oxygen uptake of the four groups.[1]

In neurotic patients without the syndrome elevated blood lactate and increased oxygen debt after exercise have also been observed commonly, but not consistently, and these may vary somewhat with the type of neurosis.[8,12,13] In manic-depressive states and in schizophrenia, postexertional elevated lactate and pyruvate levels have been found with more consistency.[9,14-17]

Similar biochemical abnormalities are seen in certain clearly organic disorders. Elevated blood lactate or increased oxygen debt (or both) after exercise have been found in infectious hepatitis,[18] anemia,[19] congestive heart failure and some types of pulmonary disease.[20] Jones and Scarisbrick[21] describe a normal subject who later contracted influenza and developed markedly diminished exercise tolerance with the infection. It is of interest that during both illness and good health this patient stopped exercise at about the same levels of blood pH and lactate, although these levels were reached much sooner during his illness.[21]

Consideration of the disorders listed above — neurocirculatory asthenia, psychiatric illness and medical disease — demonstrates a common denominator in abnormal carbohydrate metabolism during exercise. The lack of specificity of this aberrant response may represent a major physiologic derangement that occurs in response to many types of stress.

Conclusions

The data of the present study show that neurocirculatory asthenia is a symptom complex associated with many psychiatric illnesses. A deficit in carbohydrate metabolism may account for some of its symptoms; the origin of this deficit is uncertain and requires further investigation. The physiologic and biochemical disorders that have been described — especially the latter — are not specific and occur in many organic and psychiatric illnesses.

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MEDICAL PROGRESS

AIR POLLUTION

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BOSTON

IF man were not so gregarious we would not have half the bother we do from air pollution. Our industrial civilization makes it economical and convenient to build larger and larger cities in smaller and smaller areas, and to design assembly plants employing thousands to make better automobiles to go faster and carry more people.

The sins of emission of the New England village, "pop. 900," are no problem. Such a town needs no central water supply or sewage system but welcomes community powerlines and telephone, and likes to be near the major highways. The village can become a thriving mill town in an astonishingly short time. A little prosperity attracts people who want work and a place to live in. Soon the young city is forced to put in a modern water supply and a sewage plant. Until it grows to about 25,000 or more it is unlikely to have an air-pollution problem. What the critical size may be depends on the climate, the geographic location, the fuel used and the industry. One cannot pinpoint the critical size because it is too easy to look about and find exceptions to any arbitrary ruling.

Air pollution is one of the diseases of increasing population.[1] Older cities, notably London, have had the problem in varying degrees for centuries. It did not assume serious proportions until well after the Industrial Revolution (1870) since when there have been a fair number of protracted "smogs" in London, each exacting a toll of deaths markedly in excess of the normal. From December 5 to 8, 1952, London had its record four-day "pea-souper," which was responsible for some 4000 deaths among its population of about 8,000,000. The full accounts,[2] with autopsy data, are unique in that they give morbidity, mortality and air-pollution data, with meteorologic conditions before, during and after the episode.

Previous lethal fogs had been in the Meuse Valley area of Belgium in November, 1930,[3] and in Donora, Pennsylvania, near Pittsburgh, in late October, 1948.[4] The general patterns of illnesses and deaths, including age distribution, were alike in all three, but Meuse Valley killed only 63 people, and Donora 22 compared to London's 4000. All age groups in London showed some increase in death rate, but those over forty-five suffered most. Table 1 (from the official report[2] on the London fog) compares deaths in London during the week of the fog and the previous week.

TABLE 1. *Deaths in London during the Fog in December, 1952.*

CAUSE OF DEATH	WEEK OF FOG	PREVIOUS WEEK
	NO. OF DEATHS	NO. OF DEATHS
Respiratory tuberculosis	77	14
Cancer of lung	69	45
Vascular lesions of central nervous system	128	102
Coronary-artery disease	281	118
Myocardial degeneration	244	88
Influenza	24	2
Pneumonia	168	45
Bronchitis	704	74
Other respiratory diseases	52	9
Motor-vehicle accidents	4	8
Suicide	10	10

One doctor practicing in a London suburb reported that 90 per cent of his patients bothered by the fog were over fifty and that the commonest signs and symptoms arose from the following: mucosal irritation, producing cough and sputum; bronchial obstruction, causing dyspnea, cyanosis and loud rhonchi; cardiac failure in the more elderly; and fever and constitutional upset.

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Etiology of Smog Disasters

In retrospect it seems strange that health authorities took no air samples at the height of the Meuse Valley and Donora smogs. The reason is simply that there was no true appreciation of what was happening until after the event. In Britain, on the other hand, routine sampling and analyses were being done before, during and after the smog — a practice established some years before.

During the 1952 smog, sulfur dioxide gas rose from a normal (for London) of 0.1 to 1.34 parts per million, and smoke (as weighable material caught on filter paper) from an expected 0.2 mg. to 4.46 mg. per cubic meter. Taken by themselves neither of these pollutants can be said to be responsible for London's increased deaths. There is plenty of evidence that man can tolerate in industry such pollution without giving it much thought except for the general nuisance. But the London values cited represent decidedly abnormal conditions. Also, increased mortality and morbidity followed closely the increase in pollution as reported. It may be significant that the work of Amdur et al.,[5,6] at this school, shows that even healthy persons give a measurable response to low concentrations of sulfur dioxide and to sulfuric acid mist as determined by the respiratory pattern.

In the Meuse Valley and at Donora it is likely that a combination of pollutants, which may have been quite different from those in London, were responsible for the irritating effect of the smoggy air. The pollutants probably included some hygroscopic materials that accentuated the natural fogs and helped stabilize its blanketing effects. Likely contributors were small amounts of soluble chlorides and possibly fluorine compounds.[7]

A feature of the London fog that is not experienced in America was its extraordinary opacity. It was thick, murky, impenetrable and very wet; it had a characteristic odor and even taste. Traffic was at a standstill. Doctors could not visit their patients in the usual fashion, and ambulance service was grossly inadequate.

Londoners used to look on these pea soupers with a sort of friendly familiarity not shared by strangers. A nice story is told of two English gentlemen who collided while walking in the 1952 fog in Hyde Park, ordinarily a delightful place containing a sizable meandering lake, the Serpentine. With the formal politeness characteristic of the English, one said, "I beg your pardon. Can you please tell me where I am going?" The other replied, "Yes, I can — into the Serpentine. I have just come out."

After this great fog Londoners took a good while to clean up both inside and outside their houses. The greasy, oily, black mess deposited made the cleaning job long and expensive. As a visitor in the spring of 1953 I discussed these mundane aspects with colleagues, with housewives and with governmental officials. The memory of the event was still fresh. I am sure that nothing remotely approaching it has been experienced in the United States. Judging by the reactions to the Donora episode, to the troubles in Los Angeles and to those currently in the area of New York City to Elizabeth, New Jersey, I do not believe that Americans would accept such visitations with the forbearance shown by Londoners.

Sir Hugh Beaver,[8] chairman of the Parliamentary Committee on Air Pollution, quotes a paragraph from a report of thirty-three years ago: "No Government has for many years taken any action with the exception of appointing committees whose labours have led to little or no result. . . ." The Beaver report,[9] published in 1954, is not at all that kind of document. It does not sidestep the issues. It spells out clearly the chief causes — inefficient open coal fires — and shows what can and must be done promptly and what should be done in the near future. It is perfectly clear that the remedy is not an easy one and that it will mean expense and bother to many and a drastic change in heating methods.

Inversions

One must consider the difference between what nature contributes and what man adds to bring the sum total up to a severe fog or smog level. Of the two, nature's contribution is the more important and, at this age, one can do nothing about it except to forecast the event. Large cities like London, Paris, New York, Chicago, Pittsburgh, Los Angeles, San Francisco and Seattle grew originally because of natural resources and navigable water for transporting raw materials and finished goods. Their climates are favorable, and when he has behaved reasonably, man has thrived in all these cities. All of them, and many others, occasionally experience very stable, quiet atmospheres with temperature inversions — instead of cooling at about 5.5°F. for each 1000-foot rise the air temperature gets a little warmer up to a maximum height of anything from about 300 to 3000 feet. Such an inversion puts on a ceiling or lid whose boundary is just as clearly defined as that of the clouds. During inversions, there is little or no wind, and the plume from a smoky chimney cones out in a horizontal stream. In contrast the smoke stream in turbulent atmospheres starts to break up on emerging from the stack.

Some forty years ago a famous smelter company was haled into court because of its stack effluents. The owners told the manager to follow the weather, to operate full swing in turbulent weather and to reduce his fires on stagnant days. The manager answered caustically to the effect that he was not a sea captain. Ever since, this has been known in metallurgical circles as the "sea-captain" method and is the engineer's humble acknowledgment that he cannot change the weather.

There is nothing in the least unhealthful about a

temperature inversion per se. The diurnal inversions in Los Angeles and the frequent "stable" spells are one of the reasons the climate is so pleasant (barring man's contributions). London's inversions are famous, but the climate, so far as nature goes, is very enjoyable. London, from March through October, is about as pleasant a climate as one can find. During the winter months the unacclimatized American shivers at the rigor of the indoor climates, but outdoor temperatures average well above those in the United States, with much smaller fluctuations.

Both the Meuse Valley and Donora episodes involved several days of heavy natural fog, inversions and industrial pollution. A recurrence of the Donora episode is unlikely if not impossible simply because the community is now thoroughly aware of the circumstances that presage danger and the industrial pollution will not be allowed to recur.

Pollutants

Atmospheric pollution implies the presence in the air of impurities in amounts above normal. This occurs with no sensible change of oxygen, nitrogen, water vapor or carbon dioxide. Pollutants can be of industrial origin, or they can come from household chimneys or from exhausts of automobiles and trucks. Under exceptional circumstances it is quite possible for concentrations outdoors to build up to levels that are objectionable or even dangerous to those who are unusually susceptible.

The most important American fuel is soft coal, but oil is a lusty competitor, with natural gas beginning to be important. The eastern soft coal contains about 0.75 per cent sulfur, mostly aspyrite, an iron sulfide. The western coals are higher in sulfur and may contain as much as 5 per cent sulfur and some fluorine. Similarly, some of the western crude oils run high in sulfur. A modern power plant burning either coal or oil emits gas from the top of the stack containing almost no carbon monoxide, runs high in carbon dioxide and low in oxygen, and contains about the same percentage of nitrogen as the air. If the plant burns furnace oil the stack effluent, like automobile exhaust, will contain considerable water vapor formed by the combustion of the hydrocarbons. Sulfur present in either coal or oil will appear in the stack gases as sulfur dioxide. This gas is invisible, has a characteristic sharp odor, irritates the nose and throat at levels of around 15 parts per million or more and is irrespirable at about 100 parts per million (or 0.01 per cent by volume), but is detectable by most persons at about 1.5 parts per million. Green plants begin to show burning by sulfur dioxide in concentrations upward of about 0.25 parts per million — long before man is bothered.

In London there are two large power plants burning soft coal with sulfur content of about 1.5 per cent. When the plants were planned it was decided that the stack gases should be scrubbed to reduce sulfur dioxide emission to 35 parts per million — a severe ruling. In contrast, the new code in Los Angeles permits 2000 parts per million at the top of the stack. A recent paper by Rees,[10] of the British Electrical Authority, tells of the ban put on scrubbers during World War II because the effluent streams were steamy and made good beacons for enemy aircraft. Rees claims that there is insufficient evidence to justify a return to the prewar scrubbing and that nobody can measure the difference, chemically or by health surveys, whether or not the sulfur dioxide is scrubbed out. Since the scrubbing is very costly the power plants would like to abandon it.

A few years ago the authorities in Los Angeles complained that their smogs were accentuated by sulfur dioxide from burning of the crude-oil flares in the refineries in the area. The flares burned off hydrogen sulfide to sulfur dioxide and water vapor. The refineries agreed to desulfur their crude oil within the plants and proceeded promptly to do so at very considerable expense and thereby recovered a substantial tonnage of high-grade sulfur. Sulfur dioxide gas is mildly reducing. A characteristic of the Los Angeles smog is its high oxidative power, which the sulfur dioxide, in some measure, nullifies. There is some doubt, therefore, whether removal of the sulfur from the oil being refined in the Los Angeles area improved conditions. It may even have made them a little worse. Nonetheless, the refineries handling "sour crudes" (high in sulfur) are universally taking steps to desulfur at the plant and thus to recover sulfur that would otherwise be wasted.

Much copper, zinc and lead is derived from smelting of the sulfide ores of these metals. The sulfur is roasted off and discharged as sulfur dioxide gas from very high stacks—500 and even 600 feet—or the gas is cleaned, concentrated and converted into sulfuric acid. The cleaning of smelter gases can usually be made to pay for itself in materials recovered and so is not, commercially, a burden on the plant.

The modern power plants are usually close to large cities and on navigable water. Smelters, on the other hand, are located according to sources of raw materials and the market for the finished metals. Often, they are at some distance from large centers of population.

Steel mills and blast furnaces handle immense quantities of raw materials and have a history of dirtying the neighborhood with fine iron ore, which is commonly a rust color, and with ash and carbon particles. This era is about ended. Modern steel mills and blast furnaces are accounting for their stack effluents and will clean them to a reasonable degree before discharge. The gas from blast furnaces, which is rich in carbon monoxide, is cleaned and used as fuel, usually right in the plant. The city of Pittsburgh, with its steel mills, is justly proud of what it has accomplished recently in cleaning up its air. It now points with pride, and a certain sly amusement, to the

fact that a transatlantic plane recently was unable to land anywhere near New York or Boston because of poor visibility but was accommodated with acclaim by Pittsburgh (which had no customs office!).

Stack emissions of fluorine in the form either of silicon tetrafluoride, a white powder, or of hydrofluoric acid gas are well known in the electrothermic production of elemental aluminum. They can cause considerable trouble in the neighborhood, especially to cattle. The fluorine evolved can be picked up by vegetation, such as grass and hay, which is eaten by cattle. There have been several outbreaks of fluorosis in cattle grazing in the vicinity of these plants.

At present a growing phosphate-fertilizer industry uses substantial tonnages of sulfuric acid to treat its raw material, phosphate rock. The rock used is largely the mineral apatite, a calcium fluophosphate. When treated with strong sulfuric acid the mineral is broken up, and some fluorine compounds are evolved.

Capture and disposal of the fluorine is now being required. This increases production costs but cannot be evaded since the pollution problem would otherwise be too serious.

Los Angeles Smog

The eye smarting in Los Angeles smog is annoying even if it has not been shown that the smog has damaged health. Certainly, it is interfering with the ordinary business and pleasures of life, giving reason enough for the vigor of the complaints.

Nature endowed this area with a very pleasant and mild climate—provided one enjoys dwelling in a sort of idyllic and beatific monotony of pleasant weather. The temperature inversions are common for about half the year, winds are usually of low velocity, and turbulence, which might dispel undue pollution, is generally absent. Rains and storms are fairly seasonal and not irregular like those in the East.

The city has grown at a rate that is nothing short of fantastic. If it continues in its present growth it will soon be the largest in the country. Its area is huge and sprawling, like that of London, but unlike London, it transacts its business and moves its workers and its goods almost entirely by automobile and truck. Virtually no coal is used, natural gas is plentiful, and both fuel oil and gasoline are burned up at a rate vastly in excess of anything known in the East.

The severity of a Los Angeles smog varies more or less with its oxidizing effect. Haagen-Smit[11] measures this by bubbling smog air through buffered potassium iodide solution, which is oxidized with liberation of iodine. He and his colleagues devised a simple, practical appraisal of the oxidizing power of their smoggy air by exposing to it test strips of unvulcanized rubber, which cracks on exposure to severe oxidants, especially ozone. They showed that initial cracking of rubber during a smog can be as short as four minutes whereas normally it would be forty-five to sixty minutes. Sunlight plays an essential part in this vigorous oxidation as evidenced by the fact that it is almost absent at night.

In the photochemical oxidation with nitrogen dioxide and organic substances, like gasoline, ozone can be formed in concentrations as high as several parts per million. This reaction accounts, in large measure, for the eye-irritating properties of Los Angeles air and for the cracking of rubber. It is accentuated by the unburned vapors of modern gasoline, high in olefins and branched saturated hydrocarbons, as compared with motor fuels commonly in use twenty years ago.

About a year ago the governor of California suggested that the oil industries of the State should close down for a few days to prove whether or not they were responsible for the smog. It would have been more to the point to ration gasoline and otherwise curtail automobile traffic—but that would have been political suicide. The oil industry's reluctance to follow the Governor's suggestion is understandable when it is recalled that the same plants a few years ago went to great expense to desulfur their crude products and then had research, which they had supported, show that decreasing sulfuric oxide (a mild reducing gas) in the Los Angeles air materially increased the oxidative (and smog) effects of the air.

Clayton et al.[12] report interesting observations in Los Angeles and Detroit in determining, by an adaptation of Libby's carbon-dating technic, what portion of the carbon in the air came from fossil fuels (oil, coal and gas) and what part from burning wastes in incinerators. Now, if one wants to fix the blame for the etiology of the Los Angeles or almost any other city's smogs it is practicable and safe to tag fuels like coal and gasoline radioactively and follow the analysis of the air for the radioisotope used.

In London there has been some question whether unusual sulfur dioxide and smoke came from domestic fires or from industrial sources. All evidence points to the domestic open fire as the arch offender, but the point could be settled convincingly by an adaptation of Clayton's technic.

The American automobile industry is one of the most highly competitive in existence. It is fully aware of the demand for better combustion of motor-car exhausts. At the moment it has no quick cure or detachable gadget that one can put on the exhaust of one's car to burn up excess carbon monoxide and eliminate the foul odor from deceleration of Diesel bus or truck. There has been invented a very clever catalyzing arrangement which works nicely on a lead-free gasoline, but it is poisoned by leadtetraethyl, which is commonly used in motor fuels. It is not yet applicable to automobiles.

It has been shown by Went[13] that typical smog, with eye irritation, is apt to be found wherever there is heavy traffic in modern motor cars burning modern gasoline. Using the markings on various common plants as indexes or measures of smog severity, Went

showed that the city of Paris had become smoggy and that the change in the last few years had come with the introduction of modern cracked fuels. He found the same kind of markings on plants in large industrial centers in widely scattered areas—Los Angeles, New York, São Paulo, London and Paris.[14] Also, he calls attention to what most people forget — that a certain amount of haze from the volatile organic matter from vegetation is normal and not man made. It is characteristic of lush vegetation such as that in the tropics.

Prevention

The effects of the London smog of 1952 have been likened to those of a mild gas attack. Granted that not nearly as much is known as one would like to know about substances responsible, it is known that reducing their total concentration is an effective preventive. Any reasonable measure to reduce one's breathing of the smoggy air helps. Last winter the Government supplied simple masks or respirators, which were obtainable at very low cost all over London. They were not nearly so good as the masks supplied to civilians in anticipation of an enemy gas attack during World War II, but less effective masks suffice for smog. Remaining indoors, and inactive, was recommended to older persons and especially to those with bronchitis, asthma and coronary-artery disease.

The engineer's role in preventing smogs is to achieve less pollution. This means better combustion and reduction of particulates in stack gases—less ash, less unburned carbon and so forth. In Great Britain it means drastic revision and change of the prevailing method of heating by domestic open fires. This kind of thing man will not do unless he is made to, but crowding and the building of large cities is forcing the issue. The writing of committee reports and the passing of air-pollution codes will carry one no farther than the pressure of public opinion demands.

It was reported at the time of London's severe fog that the prize cattle at the Smithfield Show were badly affected but that ordinary cattle for slaughter were not. The prize animals were kept clean, and their stalls were clean. The ordinary ones, on the other hand, stood in the familiar aroma of the barnyard in which ammonia is commonly in fair concentrations. This ammonia, it was assumed, neutralized both the sulfur dioxide gas and sulfuric acid mist.

Carrying this idea a step farther it is suggested by Wilkins[15] in London that an adjustable wick dipped into a bottle of ammonia serves as "an elegant alternative to an indwelling pig." A report is also given of the effectiveness of a damp baby, something no mere engineer would venture to suggest.

This country has not had any incidents to compare with London's, but it would be folly not to take the eye smarting in Los Angeles and in the New York City and New Jersey areas as warnings and heed them. Pittsburgh showed what could be done. It is not clean yet, by any means, but it is vastly better than it used to be and probably is better than any other heavily industrialized area.

It is no simple matter to keep people from crowding into cities. The chambers of commerce and the city administrations want their communities to grow, and they do all they can to bring in new residents. Soon they get into the predicament of Los Angeles, which probably would be glad to speed the parting guest but does not quite dare say it aloud.

In *Innocents Abroad* Mark Twain put this very aptly when describing a small town in Italy:

> The people here live in alleys two yards wide, which have a smell about them which is peculiar but not entertaining. It is well the alleys are not wider, because they hold as much smell now as a person can stand, and of course if they were wider they would hold more, and the people would die.

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MEDICAL INTELLIGENCE

MANAGEMENT OF SEVERE HYPERTHERMIA WITH CHLORPROMAZINE AND REFRIGERATION*

Report of a Case

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CONSIDERABLE interest has recently centered around the use of chlorpromazine in medicine. Many of the properties of this drug have been studied, and its use in clinical practice in this country in such conditions as the management of vomiting, hiccups, mental and emotional disturbances, intractable pain and alcoholism has frequently been discussed in the literature. Undoubtedly, the possibilities of chlorpromazine have not been exhausted, and it bids fair to achieve dramatic results in other major applications. In France its surgical indications have been particularly emphasized, for under the name of "artificial hibernation" Laborit and Huguenard[1,2] introduced it as an antishock agent and a useful adjunct to major surgery in the poor-risk patient. The hypothermic action in conjunction with refrigeration is remarkable and has been studied in France[3] and Canada[4] and recently in this country.[5] Moreover, this hypothermic effect may be utilized in the management of the dangerous hyperpyrexia encountered in medical patients. The following case is an example of the life-saving effect of chlorpromazine in severe hyperthermia.

CASE REPORT

A 52-year-old woman was admitted to the Springfield Hospital, on October 6, 1954, because of paralysis of both lower extremities of 8 years' duration. In addition she complained of paresthesias of both legs and impairment of vision. A diagnosis of multiple sclerosis had previously been made in another hospital.

Physical examination showed a spastic paraplegia, a bilateral Babinski sign and clonus. The patient was totally disabled. Further neurologic investigation elicited nystagmus, retrobulbar neuritis and intention tremor. The patient complained of frequency. Urinalysis was reported as negative. She was transferred to the Chronic Service, where physiotherapeutic measures were instituted. After the insertion of a retention catheter a mild urinary-tract infection developed. The urine gave a +++ test for albumin, and the sediment was loaded with white blood cells. This infection was readily controlled with antibiotic therapy.

The patient's stay in the hospital was uneventful until 4 months after admission, when a headache and a temperature of 100°F. developed. On the following day hematologic studies revealed a white-cell count of 21,750, with 89 per cent neutrophils. The urine was cloudy, and gave a +++ reaction for albumin. The sediment contained many white blood cells in clumps, but no casts were seen. On the evening of the same day she complained of severe malaise, and the temperature rose to 104°F. (Fig. 1). Penicillin and streptomycin were administered. During the next morning she was restless and somewhat confused. The temperature was 104°F. at 3 a.m. and 1 hour later reached 106.6°F. The pulse was thready at a rate of 152. At 5 o'clock the temperature reached 107.8°F. by rectum. She was now comatose. The pulse was weak and rapid, and the respirations shallow and frequent. Physical findings were unchanged from those on admission. The lungs were clear, and there was no nuchal rigidity.

Because of the apparently poor prognosis, it was believed that heroic efforts would be required to control threatening

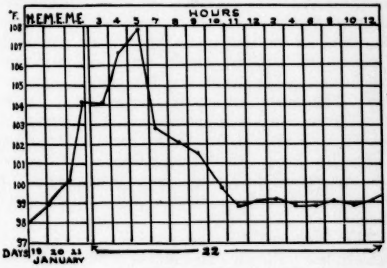

FIGURE 1.

overwhelming hyperthermia. On the basis of the experimental and clinical studies of the French workers[2,3] it was decided to use chlorpromazine‡ together with refrigeration to induce the so-called "artificial hibernation." Accordingly, an infusion of 50 mg. of the drug in 1000 ml. of 5 per cent glucose in distilled water was started intravenously. Half an hour later, ice bags were applied to the groins, axillas, precordium and forehead. The temperature chart (Fig. 1) shows the effect of this procedure on the temperature, which dropped to 102.6°F. at 7 a.m. The pulse was 92, and the blood pressure 86/40. One hour later the temperature was 102°F. Shivering did not occur at any time during the period of therapy with chlorpromazine, though the patient was closely observed for this symptom as an indication for further dosage of the drug.

At 8:30 a.m. another 50 mg. of chlorpromazine in 5 per cent glucose in distilled water was administered. Half an hour later the patient began to respond and to answer questions logically. Oxytetracycline was administered intramuscularly. The ice bags were removed. The temperature had fallen to 99.8°F. at 10:00 a.m. and remained constant. For the remainder of the day she was conscious and afebrile and resting comfortably. The blood pressure rose to 110/70.

A lumbar puncture was performed, and the laboratory findings revealed 16 fresh red blood cells per cubic millimeter and a total protein of 68 mg. per 100 ml. No white blood cells were seen. A culture of the spinal fluid was later reported as negative. Culture of the urine grew *Aerobacter aerogenes*. This organism was found to be slightly sensitive to chloramphenicol and resistant to streptomycin, penicillin, chlortetracycline, oxytetracycline, tetracycline, polymyxin and nitrofurantoin. The nonprotein nitrogen was 28 mg. per 100 ml. A blood culture showed no growth. A film of the chest taken with a portable machine was interpreted as normal.

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‡Kindly supplied as Thorazine by Smith, Kline and French Laboratories, Philadelphia.

On the following day at 2 a.m., 25 mg. of chlorpromazine was again administered in 1000 ml. of 5 per cent glucose in distilled water. The temperature, which had remained at 99°F., had risen to 100.2°F. by evening. The blood pressure was 110/70. The range of the temperature curve during the following days is given in Figure 2. After intravenous administration chlorpromazine was given intramuscularly in doses of 25 mg. 3 times a day. Later, the drug was administered orally.

After receipt of the laboratory report of the sensitivity of the organisms cultured from the urine, oxytetracycline was replaced by chloramphenicol. With the use of this antibiotic, the fever decreased, and the temperature returned gradually to normal levels. The nonprotein nitrogen was now 28 per 100 ml. The white-cell count was 8950, with 71 per cent neutrophils. The urine was free of albumin, and the sediment contained 2 to 4 white blood cells per high-power field.

Eleven days later the patient was discharged at her own request. Arrangements were made by her husband to care for her at home. She no longer complained of the leg pains, which had been present before admission and before the use of chlorpromazine.

Discussion

The threat of irreversible brain damage as a complication of hyperpyrexia can pose a serious problem to the clinician. This case illustrates the use of chlorpromazine in conjunction with refrigeration as a hypothermic agent in the management of a severe hyperpyrexia. Apparently, the urinary-tract infection was secondary to an indwelling catheter. Pyuria, leukocytosis and fever were present, and *A. aerogenes* was cultured from the urine. The administration of chloramphenicol produced a prompt therapeutic response. In multiple sclerosis, however, the possibility of an acute exacerbation of the disease, involving the thermoregulating center, must be borne in mind. The patient's disease may have been responsible for the abnormal hyperthermic reaction to infection. The use of an effective hypothermic agent to control the high temperature provides time for treating the causal phenomenon. It is believed that chlorpromazine, in conjunction with refrigeration, enabled this patient to survive until antibiotic therapy became effective.

Fever may be an aid to the body, even in the absence of adequate confirmation, in its fight against infection. However, when it occurs to such a marked degree, it should be looked upon as detrimental in itself, by threatening the functions of vital tissue.

The physiologic mechanism of the hypothermic effect of chlorpromazine is not completely understood. The Europeans, and particularly the French school, claim that chlorpromazine has both central and peripheral actions. According to Laborit,[6] increase of thermolysis is responsible for the hypothermia when the thermoregulation is blocked by the central action of this drug. It has a central action at the level of the hypothalamus, depressing the response of the autonomous nervous system as well as the temperature-regulating mechanism. The homothermic person is made poikilothermic, and defense against hypothermia induced by the cooling is made impossible. There is therefore no increase in the metabolism or in the oxygen consumption and shivering. As stated by Dundee and his co-workers,[7] "Man is equipped with a highly effective mechanism for combatting the effects of cold and the first step in the production of hypothermia must be to overcome this response. This can be achieved by the deep anesthesia, the use of muscle relaxants, or by the 'lytic cocktail'." The last includes chlorpromazine, promezathine, meperidine and diparcol. The same authors compare the efficiency of chlorpromazine in lowering body temperature with that of the commonly used antipyretic drugs. Of the drugs studied, chlorpromazine alone possessed the ability to produce vasodilatation and to

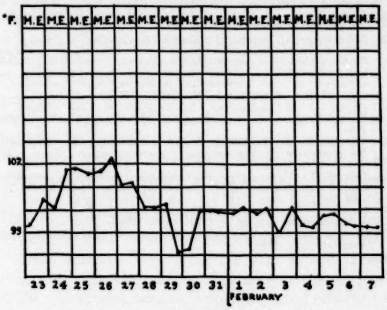

Figure 2.

inhibit shivering. It was found to be the most effective drug to aid in the production of hypothermia. Its peripheral action causes vasodilatation, facilitating the loss of heat when cooling is applied.

Moreover, the application of external cooling without chlorpromazine would be a stress, particularly for a severely ill patient, and would be unable to induce such a marked and abrupt drop in temperature.

Experiments on rats at Rhône-Poulenc Laboratories,[8] using a control group, showed that the animals receiving chlorpromazine and exposed to hypothermia had a striking decrease in the consumption of oxygen and a marked degree of hypothermia. When the oxygen consumption of the control animals was increased, there was no significant drop in their temperatures.

In the case presented above, chlorpromazine was used with the sole purpose of returning the temperature to normal limits. It was not necessary to induce a true hypothermia, or the so-called "artificial hibernation," because the patient improved when the hyperpyrexia was controlled. Furthermore, it appears that better results can be achieved if promezathine, meperidine and diparcol are combined with chlorpromazine to produce the "lytic cocktail."

Summary

A case of severe hyperthermia, secondary to a urinary-tract infection in a patient with multiple scle-

rosis, is reported. The use of chlorpromazine in conjunction with refrigeration was life saving. The action and effect of this drug as a hypothermic agent are discussed. It is suggested that chlorpromazine may prove to be a useful addition to the therapeutic armamentarium for the management of severe hyperpyrexia.

I am indebted to Dr. Howard Kennedy for suggestions and encouragement.

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DOCTORS AFIELD

Georg Büchner

Heinrich G. Brugsch, M.D.*

BOSTON

On February 19, 1837, Georg Büchner, physician, scientist, political refugee and poet, died in Zurich of typhoid fever. He was then only twenty-three years and four months old, but his remarkable poetical talent had already been recognized in his drama, *Danton's Death,* published in 1835, and became even more apparent when two plays, *Leonce and Lena* and *Woyzeck,* were published posthumously. His most recent biographer, Knight, states that Büchner showed "more unmistakable signs of genius than any other writer in the German language, Goethe excepted." In addition Büchner was a remarkable man who, still a medical student, was recognized as an exponent of a group of German fighters for freedom as well as a promising scientist.

Georg Büchner was born on October 17, 1813, in the small town of Goddelau near Darmstadt, the son of a physician. His father and his paternal grandfather were city physicians in the Grand Dukedom of Hesse, whose capital, Darmstadt, at the time of Georg's school days (1830), numbered 21,000 inhabitants. His maternal grandfather was a hospital administrator. One of Georg's brothers, Ludwig, who also became a physician, was the author of a popular philosophic book, *Kraft und Stoff,* in which he expressed such a materialistic point of view that he had to resign his post as a teacher of medicine at the University of Tübingen. Georg followed his father's wish when he began his study of medicine in 1831 at Strasbourg, where he soon became interested in the natural philosophic discipline then greatly advanced by the work of Cuvier, Carus and Oken. After two years of study in Strasbourg, he returned to the University of Giessen, his state university, in compliance with regulations limiting studies at foreign universities to two years. While at Giessen he became more and more concerned with the political problems of his homeland, which then suffered greatly under inept leadership. In 1834 he wrote a revolutionary manifesto as well as his first play and narrowly escaped arrest and imprisonment. In March, 1835, he returned to Strasbourg, this time as a refugee indicted for high treason.

Again he devoted his studies to medicine and biology, and on April 13 and 20 and May 4, 1836, he read to the Société d'Histoire Naturelle de Strasbourg a paper entitled "Sur le système nerveux du barbeau" based on careful anatomic studies of the nervous system of the barbel and related fishes. This paper was immediately recognized as a valuable addition to the growing knowledge of comparative neuroanatomy, and he was not only elected a member of the Strasbourg academy but also made a doctor of philosophy at the University of Zurich, then newly founded, and an asylum to many oppressed and expelled Germans. After some difficulties he was able to leave Strasbourg for Zurich. In November, 1836, at the age of twenty-three years, he was appointed privatdozent (instructor) to the Faculty of Liberal Arts after a "Probevorlesung" on the cranial nerves. He then began a lecture course on comparative anatomy of the fishes and amphibia, which he based upon his own anatomic preparations. According to the recollections of one of his students he was a well versed, matter-of-fact lecturer. However, before this course was finished he became sick on February 2, 1837, from typhoid fever, then widespread throughout Europe, and died seventeen days later despite the devoted care given him by one of the best clinicians of those days, Schönlein, then professor of medicine in Zurich.

Büchner, as physician and scientist, is now almost forgotten; the poet, however, will live long in German literature, for this outspoken, somewhat pessimistic and restless fighter for happiness described, for the first time since Goethe, human suffering in a straightforward, often unbridled, but poetic and original language.

His medical background is apparent in many of his writings. Psychiatrists will still read with interest his novel, *Lenz.* Here he described vividly and with

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remarkable insight the seizures of the schizophrenic poet, Lenz, a friend of Goethe, who sought refuge in the house of the minister, Oberlin, but could not stay on account of his uncontrollable attempts to run away and to threaten suicide and his tendency to frighten people.

Büchner's most mature work, *Woyzeck,* is still of interest and served as a libretto for the opera *Wozzeck,* by the composer, Alban Berg. In it he takes issue with the medical opinion rendered by a contemporary physician and teacher, Johann Christian Clarus, in a murder case. Clarus had rejected the possibility of insanity as the motive for the action of a simple-minded soldier who, in a fit of loneliness and rage, killed his sweetheart after she deserted him. Clarus's opinion was accepted by the Court, and the soldier executed. Büchner, in his drama, takes issue with this verdict and shows remarkable insight into the tragic and helpless fight of a lonely man to deal with forces outside his control. He was well aware of the misery among the underprivileged classes of his days and minced no words about it. He once remarked, "It is easy to be an honest man if one has his daily soup, vegetables and meat for food." His political manifesto, *Der Hessische Landbote,* distributed and printed secretly in 1834, expresses his sentiments best, although the published version was altered by others. He discussed in detail the cruel and senseless form of taxation, common in his day, whereby the poor were taxed without voice in the elections and where the privileged classes owned the land. He called for the formation of secret societies through which the masses could be reached and for the replacement of monarchies by a republic. He was, however, well aware that the time was not ripe and his fellow citizens not ready for radical changes. The manifesto appeared in March, 1834, but found little response among those for whom it was written. Soon the plotters were denounced; some were arrested, and others fled, among them Georg Büchner. Several of his compatriots went to Strasbourg or Zurich; others, such as Minningerode, who later became a minister in Virginia, immigrated to the United States. Büchner, too, was intrigued by the land across the sea, and his fellow students in Giessen, who disliked his straightforwardness and revolutionary ideas, called him "the preserver of the European equilibrium, the abolisher of the slaves." However, his literary friend, Gutzkow, insisted that he remain where he could write in his native tongue, and so he chose to go to Zurich, the city where Oken taught (another upright man who twice had lost his professorship because of his beliefs). Büchner's life was a restless one after he left his home. He fought deeply against a sense of frustration and depression because of the aimlessness of his time, the disunity of his country and the lack of understanding among the educated for the lot of the underprivileged. He was tolerant toward religious thoughts but unable to see the world order as an acceptable one and one worth living in, but as his friend, Becker, saw him, "When he spoke and raised his voice, his eyes shone — I did not believe it any other but the truth. What would I not have done for him, of what would he not have convinced me!"

When Büchner was dying his fiancée and friends were with him. In his fever fantasies all the anxieties of the persecuted became apparent, until shortly before death, he found peace in the recognition that life means suffering, but also that suffering brings peace. "We do not have enough pain, we have too little, since we go to God through pain — we are death, dust, ash, how could we complain?"

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42091

PRESENTATION OF CASE

A sixteen-year-old schoolboy entered the hospital because of back pain.

For about a year he had experienced a nearly constant aching discomfort in the back that was made worse by exercise and often kept him from sleeping at night because he was unable to find a comfortable position. Occasionally, there was also pain in the lateral aspect of the right thigh. The symptoms had been somewhat worse in recent months. The pain was aggravated a week before entry after he had fallen on his back while playing football. At this time he first noted a slightly tender lump in the right lumbar paravertebral area. There had been no weight loss, malaise or other symptoms.

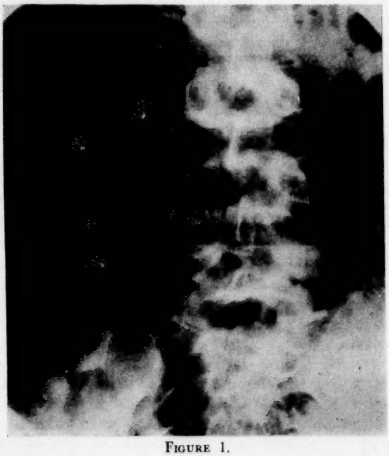

FIGURE 1.

Physical examination revealed a well developed, well nourished boy. An ill defined, soft, firmly fixed, nontender, nonfluctuant soft-tissue mass, measuring about 8 cm. in diameter, was present in the right lumbar paravertebral area. Examination of the heart, lungs and abdomen was negative.

The temperature was 97.2°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 ml. and a white-cell count of 10,600, with a normal differential. X-ray films of the lumbar spine showed a large area of bone destruction of the fourth lumbar vertebra involving the right posterior portion of the body, the right transverse process and the right pedicle (Fig. 1). Extending to the right of this vertebra was a mass within which there was scattered trabeculated calcification, especially in its rim. X-ray films of the chest were normal.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD B. D. NEUHAUSER*: This is an extraordinarily brief protocol, and gives me no difficulty in recognizing the site of the trouble. I shall have difficulty in identifying the abnormality that was present. In the x-ray films, which are overexposed and show a considerable amount of gas in the bowel, there is a lesion localized to the right aspect of the fourth lumbar vertebra that contains an area of active bone destruction where the general architecture involving the right lateral and posterior half of the vertebral body is distorted. The right pedicle of that vertebra is almost completely destroyed, and the transverse process has been lost; practically no remnant of it can be seen, although with the spotlight it can be visualized. There is a vaguely defined soft-tissue density, the characteristics of which are to a great extent obscured by the overlying gas; therefore, I have no opportunity to determine the density of the soft tissue, whether it is of water or muscle density or of density less than that, which might be produced by fat, for instance. One can pick out density greater than muscle density on these films and recognize that the apparent periphery of the soft-tissue mass is outlined by calcific deposits. There is a thin line, and scattered through the mass there appear to be other fine, linear streaks and flecks of calcific density. Radiating upward from the right side of the body are a few streaks of calcific or bony density that are somewhat different in character in that they are coarse rather than fine densities and extend outward. I do not know whether the deposits are merely calcium or bone. There was no evidence of systemic disturbance.

The next step is an attempt to find out the nature of the lesion. I think that I can only hazard a guess

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about the statistical possibilities, because the pictures, particularly of mass lesions in this area, vary greatly. There may be identical lesions with varying x-ray appearances or varying lesions with the same x-ray appearances. They all overlap, and all may mimic each other. Therefore, it is often difficult or impossible to make a specific diagnosis, but it is interesting to try.

Whenever I am presented with a lesion that appears to be primarily osseous I try to decide in my own mind whether it is a malformation of bone, an inflammatory process, under which I include a granulomatous process, or a neoplasm. There is no point in discussing such processes until I have decided into which of the three the lesion falls — that is, there is no point in my jumping to a decision about whether this was a benign or a malignant neoplasm or a primary or secondary one until I have decided among those three. I think there is practically no chance that this was a congenital malformation of bone. The process developed during the year before admission and destroyed bone.

Could it have been an infection? It was certainly not osteomyelitis of the ordinary type, which should not as a rule produce this picture. If it had been, the soft-tissue mass would have had to be an abscess, and should have given more evidence of an acute inflammatory process. However, some benign infections will produce a tumorlike destruction, tumorlike soft-tissue masses and calcification; these are the lesions due to coccidioidomycoses or torula — the granulomatous lesions. Eosinophilic granuloma can at times look like a neoplasm. However, I doubt if this was an infection, for there was no systemic evidence of infection; no other lesion was present, and the chest was clear.

A number of tumors develop in the spine, particularly in the young; I think I have to include this sixteen-year-old boy in the adolescent age group. Sarcomas and primary bone tumors are rare. They usually cause considerable destruction of bone, eventually produce a soft-tissue mass and usually are not characterized by a calcified periphery in the soft-tissue mass. Fibrous dysplasia — not a true tumor, of course — will also on occasion produce expansion of the transverse process, with a thin shell of bone at the periphery, but I have never seen such a lesion grow as large as this or cause such a large soft-tissue mass. Soft-tissue tumors occur in that neighborhood quite frequently in this age and may secondarily invade or erode bone. They may be roughly grouped as belonging to the neurogenic group — the neuroblastomas, neurofibromas, neurofibrosarcomas and similar lesions. This lesion appears to have begun in or close to the transverse process, which is the central point of the lesion; destruction extended into the body and the mass extended out into the soft tissue laterally and posteriorly — all of which is against a neurogenic tumor.

One of the commonest tumors that arise in a transverse process or in a pedicle and frequently invade all portions of the bone is one that has puzzled me greatly because our pathologists give it a different name every time they see one; that is the giant-cell tumor of the spine. It appears to be entirely different from the giant-cell tumor in the long bones in its behavior and in its clinical pattern. Giant-cell tumors in the long bones are uncommon while the epiphyseal lines are still open; they usually occur as the epiphyseal lines are closing or are closed. But that is not true of the so-called "giant-cell tumor" of the vertebra or one of its processes. It may occur at any age. Characteristically, it expands the bone greatly, and usually there is a very thin shelf of calcification or bone at the periphery of the mass. These can be extraordinarily large — certainly as large as the tumor under discussion; we have seen some 5 cm. in diameter. I have never seen one as large as this lesion appears to have been. Eventually, many portions of the body of the vertebra are destroyed. I think it is likely that the patient originally had that type of tumor in the transverse process, but a number of the features in the radiologic appearance of this lesion do not fit into that. The bony shell around the mass does not appear to be intact, it appears to be broken through and has been destroyed in part. The radiating spicules of bone extending outward from the lateral aspect of the vertebral body itself are not a characteristic feature of a "giant-cell tumor." One wonders whether this boy had such a lesion that presumably was benign and had undergone a malignant transformation. I think that is a remote possibility.

What other lesion could have this effect? A Ewing tumor, I suppose, could; it is usually difficult to make that diagnosis in the vertebra. We have had only 1 Ewing tumor involving the spine at the Children's Hospital; it was in an infant about a year of age and involved the second cervical vertebra. That lesion was much smaller than this. It was discovered early, for it was in an area in which lesions are easier to find than in the lumbar area. The x-ray characteristics were almost identical to those of this lesion: it was an expanding lesion about 3 cm. in diameter that involved the transverse processes; it had a thin shell of bone around it that had been broken through in part. That child was still alive nine years after x-ray therapy to the lesion. Each time that the child returns for an examination we ask the pathologist to review the slide, for we have always doubted the diagnosis, but he always confirms it.

Hemangioendothelioma of bone will occasionally produce this type of lesion, but it must be rare.

I think that the best possibility is a primary "giant-cell tumor" beginning in the transverse process, possibly with malignant transformation; the second possibility is a Ewing tumor. It was an easy lesion to locate; it was a very difficult one to define. Certainly, the next and all-important step was to carry out a biopsy so that definitive treatment could be given to the patient.

DR. BENJAMIN CASTLEMAN: Do you believe, Dr. Neuhauser, that the maxim that the giant-cell tumor does not occur before the age of twenty holds also for such tumors of the spine?

DR. NEUHAUSER: Not if they are the same tumor, but I wonder if they are the same because of the difference in their behavior. Just because a tumor has giant cells in it does not make it a giant-cell tumor. I have often wondered if the so-called giant-cell tumors that we see in the spine are manifestations of a hemangiomatous process, with a great many giant cells, but the question is certainly not settled in my mind. They behave differently, and appear at different ages, from giant-cell tumors elsewhere.

DR. CASTLEMAN: Does the so-called giant-cell tumor of the spine respond any better or any worse to x-ray treatment than those of the long bone?

DR. NEUHAUSER: They respond very well. It takes a considerable amount of irradiation — several thousand r — to produce healing. We have carried that treatment out only on tumors that could not be excised, primarily because of location. It is possible that a giant-cell tumor would become malignant later. We have treated 3, which so far have given no further trouble. The average follow-up interval has been fourteen years.

DR. CASTLEMAN: After biopsy?

DR. NEUHAUSER: Yes.

CLINICAL DIAGNOSIS

Benign tumor of spine, ?giant-cell tumor.

DR. EDWARD B. D. NEUHAUSER'S DIAGNOSIS

Giant-cell tumor of vertebra.

ANATOMICAL DIAGNOSIS

Aneurysmal bone cyst of vertebra.

PATHOLOGICAL DISCUSSION

DR. AUSTIN L. VICKERY: It was decided that a biopsy should be performed and that it should be obtained with a Silverman needle; this was done, and a presumptive pathological diagnosis of aneurysmal bone cyst was made. On that basis, an excision of the lesion was advocated, and a month later a second operation was performed. At this procedure, the tumor was extremely vascular, with a thin peripheral remnant of eroded cortical bone, much as Dr. Neuhauser has described in the films. The lesion was curetted and excised satisfactorily. The copious bleeding was controlled with Gelfoam. Microscopically, the specimen showed the characteristic features, which were also seen on the specimen from the needle biopsy — namely, large, blood-filled cavernous sinuses with an intervening fibrous matrix (Fig. 2) in which variable quantities of osteoid tissue, some partially calcified, were embedded. In addition, there were focal areas of reparative bone formation and bone resorption, but the striking feature was the presence of the large pools of blood and vascular channels, which pervaded the entire lesion and made up its pathognomonic histologic pattern. These large blood-filled spaces in the aneurysmal bone cyst give the lesion its characteristic spongy gross appearance. In addition, there were scattered multinucleated giant cells in various parts of the lesion; these, however, were never in profusion, as seen in typical benign

FIGURE 2.

giant-cell tumors of bone, and appeared to be principally in locations where one might expect to see osteoclasts — namely, where there was bone resorption and remodelling of the partially destroyed bony architecture.

Dr. Neuhauser has described a peculiar type of giant-cell tumor of the spine that does not follow the usual clinical or histologic pattern of the benign giant-cell tumor of the epiphyses of long bones; I think we are entering now into a question of semantics rather than a basic variation in opinion. This tumor, with its large blood-filled spaces and fibrous stroma, which we called an aneurysmal bone cyst, is probably not a real tumor. It is a lesion of bone that was first hinted at in 1942 by Jaffe and Lichtenstein[1] but was not described as a distinct entity until 1950 by Lichtenstein.[2] At that time he reported a group of cases, which he thought were of sufficient likeness and uniqueness to be classified separately from other solitary bone lesions. Because of its characteristics — the

cavernous blood-filled sinuses and cystlike consistence — he tentatively designated it aneurysmal bone cyst. The lesion is solitary, localized and expansile, with a spongy vascular internal structure and a thin layer of eroded cortical bone about the periphery. It tends to involve long bones, flat bones and vertebras. So far, I think it sounds much like the entity that Dr. Neuhauser referred to as an unusual vascular "giant-cell tumor" involving the spine; I have an idea that we are speaking about the same lesion and that its nomenclature and interpretation are a subject of controversy. In any event, Lichtenstein has not regarded this lesion as a true neoplasm but as probably the end result of a local circulatory malformation such as an arteriovenous aneurysm or an old venous thrombosis that subsequently may develop over a period into dilated vascular channels in a fibrous stroma, with eventual expansion and erosion of adjacent bone and encroachment upon contiguous soft-tissue structures.

Two thousand primary bone tumors were reviewed at the Mayo Clinic last year,[3] and 26 were designated as aneurysmal bone cysts. In 11 of these 26 lesions, the original pathological diagnosis had been benign giant-cell tumor, and in 9 the original radiologic opinion was also benign giant-cell tumor. The lesion occurs principally in children, adolescents or young adults, and the prognosis is good. Conservative treatment by either curettage or excision is advocated. Five-year follow-up studies of 19 of the 26 patients at the Mayo Clinic showed that all were well. There had been only 1 local recurrence. Consequently, the Mayo Clinic workers agree with Lichtenstein that these lesions should not be considered true neoplasms.

Is it possible that the aneurysmal bone cyst could represent the result of hemorrhage from trauma into a pre-existing giant-cell tumor? This certainly merits consideration and is discussed by Lichtenstein,[4] who, however, claims that in the 30 cases or more that he has had the opportunity to review, there was no history of lesions existing before the establishment of the diagnosis. He also discounts an organized intraosseous hematoma as the etiologic mechanism on the basis of an inconsistent histologic architecture.

DR. CASTLEMAN: How many reported lesions were in the spine?

DR. VICKERY: Of the Mayo Clinic group 15 were in long bones, and 5 in the spine; 4 of 17 cases of Lichtenstein[4] were in the spine.

DR. NEUHAUSER: I think we are talking about the same lesion; that is why I mentioned a hemangioendothelioma. We have seen only 1 in the long bone and perhaps 4 in the spine.

DR. JOHN D. LEIDHOLT: I was not scrubbing on the case, but I did look over the shoulder of the operator, Dr. Joseph S. Barr; the description was exactly as I saw it. It was not truly cystic in that it seemed to consist of solid material. No fluid escaped when it was opened. It was Dr. Barr's impression that ligation of the base of the tumor controlled a great deal of the bleeding.

One point that interests me is whether Dr. Vickery can tell us what the peripheral area of increased density represents on the microscopical examination. If it was bone or osteoid tissue forming under a displaced periosteum one might gain some insight into what the tumor actually represents. If it was merely calcification in the tissue, the lesion is less likely to have been a giant-cell tumor. Could you tell what was actually causing that line of increased density at the periphery seen in the films?

DR. VICKERY: I think it was eroded cortical bone that had become expanded.

DR. LEIDHOLT: Actually, the tissue was soft and could be displaced with a retractor easily. Certainly if it was bone, it was a thin, pliable layer of bone.

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CASE 42092

PRESENTATION OF CASE

An eighty-three-year-old widow was admitted to the hospital because of vomiting.

For many years she had had brief, mild episodes of vomiting often related to ingestion of spicy foods or a supine position and relieved by an upright position. Eight years before entry an upper gastrointestinal series was said to have demonstrated a hiatus hernia. During the year before admission these episodes, which became more severe and lasted for several hours, occurred every two months. There was severe vomiting of coffee-grounds material during the three days before admission. There was no dysphagia, abdominal pain, weight loss or melena.

There were several episodes of nocturnal dyspnea during the year before admission, the last occurring with the vomiting three days before entry. There was no history of cough, hemoptysis or ankle edema.

Physical examination revealed a pale, dehydrated, fatigued woman who was vomiting coffee-grounds material. The chest was emphysematous, and diaphragmatic motion was diminished. The trachea was in the mid-line. There was diminished resonance over the left lower lobe posteriorly; moist, crackling, inspiratory rales were audible over both lung bases. The point of maximal cardiac impulse was at the left anterior axillary line. There was atrial fibrillation, and the apical rate was 148. A Grade 3 apical systolic murmur was transmitted to the axilla and back. The neck veins were flat when the patient was raised to 45°. The abdomen was normal. Popliteal and dorsalis pedis pulses were absent bilaterally.

The temperature was 99°F., the pulse 80, and the respirations 16. The blood pressure was 110 systolic, 60 diastolic.

Urinalysis gave a + test for albumin; the sediment contained 3 to 6 red cells and 10 to 15 white cells per high-power field. Examination of the blood revealed a hemoglobin of 15.2 gm. per 100 ml. and a hematocrit of 49 per cent. The white-cell count was 14,900. The serum nonprotein nitrogen was 77

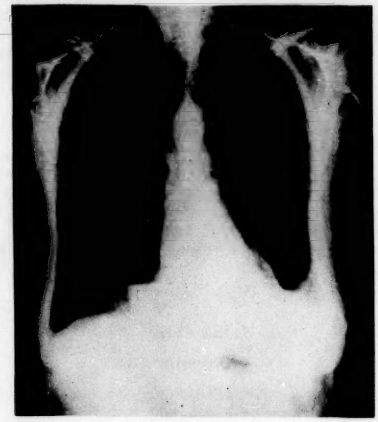

FIGURE 1.

mg., the total protein 8.2 gm., the albumin 5 gm., and the globulin 3.2 gm. per 100 ml. The serum sodium was 142 milliequiv., the potassium 3.5 milliequiv., the chloride 87 milliequiv., and the carbon dioxide 34 milliequiv. per liter. The prothrombin content was normal. The vomitus gave a ++ guaiac test. Stool specimens were guaiac negative. Sputum culture grew out abundant alpha-hemolytic streptococci and *Haemophilus influenzae,* and a few *Staphylococcus aureus* and beta-hemolytic streptococci. Urine culture grew out a rare nonhemolytic streptococcus. X-ray films of the chest and abdomen demonstrated a large fluid-and-air-filled viscus behind the heart and a small collection of air beneath the left leaf of the diaphragm. There was a pleural effusion on the left. An upper gastrointestinal series showed the fundus and probably the antrum of the stomach lying above the diaphragm. An intravenous pyelogram revealed good concentration and prompt excretion of the contrast substance bilaterally. A rounded shadow measuring 10 cm. in diameter overlay the lower pole of the right kidney. The right ureter was slightly displaced medially. There was no calyceal distortion. An electrocardiogram showed atrial fibrillation, with a ventricular rate of about 150, a QRS interval of 0.08 second, an occasional ventricular ectopic beat and a normal axis. The ST segment was sagging and depressed in Leads 1, 2, 3, aVF and V_2 through V_6.

With digitalis therapy the cardiac rate was lowered, but episodes of fibrillation persisted. Occasional vomiting continued, and large amounts of brown fluid were aspirated from the stomach. After several days the patient was able to take fluids and soft food by mouth. The temperature rose to 103.4°F. on the second hospital day and, in spite of antibiotic therapy, remained between 99 and 103°F. Gastric intubation on the second hospital day caused considerable coughing. Urine culture on the twelfth hospital day grew out abundant *Proteus vulgaris.* An x-ray film of the chest on the twelfth day demonstrated some resorption of the pleural effusion on the left (Fig. 1). The serum electrolytes were maintained at normal values with intravenous infusions of fluids. The nonprotein nitrogen fell to normal limits. On the sixteenth hospital day the patient appeared drowsy, with some epigastric discomfort and vomiting and with a temperature rise to 103°F. Examination of the lungs revealed sticky inspiratory rales in the right axilla and below the right scapula. An x-ray film of the chest now showed a well circumscribed density at just about the costophrenic sinus on the right (Fig. 2). The serum nonprotein nitrogen was 41 mg. per 100 ml. Throat culture grew out abundant alpha-hemolytic streptococci, and blood culture was negative. Parenteral administration of fluids, gastric suction and vigorous antibiotic therapy were resumed. On the twentieth hospital day the nonprotein nitrogen was 26 mg., and the fasting blood sugar 133 mg. per ml., and the hematocrit 40 per cent. Two days later the patient was somewhat disoriented and hyperpneic. Bronchial breath sounds were heard anteriorly over the right lung. The white-cell count was 31,800. On the twenty-fourth hospital day the hematocrit was 29 per cent. The serum bilirubin and bleeding and clotting times were normal. The Coombs test was negative. The serum iron was 27 microgm. per 100 ml. On the evening of the twenty-fourth hospital day there was an episode of ventricular tachycardia at a rate of 165. With intramuscular and intravenous injections of Pronestyl and intravenous administration of potassium chloride the cardiac rate reverted to an atrial or nodal tachycardia with heart block. The atrial rate was 250, the ventricular rate 55 to 72. The blood pressure was maintained at 110 systolic, 70 diastolic. The temperature continued elevated between 99 and 101.2°F. An electrocardiogram two days later showed a normal sinus rhythm at a rate of 84, a PR interval of 0.18 second and a QRS interval of 0.07 second, a normal axis, sagging and depressed ST segments in Leads 2, 3, aVF and V_2 through V_6, and prominent R waves and low T waves in Lead V_1. Because of poor nutrition and inability to take food by mouth a jejunostomy was performed on the twenty-eighth hospital day. The next day the patient vomited 500 ml. of green fluid; 600 ml. more was removed by

gastric suction. After the vomiting, rales were audible over the right lower parasternal area of the lung. About six hours later there was a brief episode of cardiac arrhythmia, and the blood pressure was 80 systolic, 60 diastolic. On the second postoperative day she was less responsive, and the respirations had increased to 46. The white-cell count was 30,000, with 97 per cent neutrophils. The hemoglobin was 13.5 gm. per 100 ml. after transfusions. Blood culture was negative. Later that day she responded only to painful stimuli. That night there was an episode of respiratory irregularity and apnea accompanied by hypotension. On lumbar puncture the dynamics were normal. The cerebrospinal fluid was clear and contained 22 red cells and 2 lymphocytes per cubic millimeter, with 30 mg. of protein and 216 mg. of sugar per 100 ml.; culture was negative. An electrocardiogram showed a normal sinus rhythm at a rate of 82, a PR interval of 0.21 second, a QRS interval of 0.08 second and a normal axis (+80°). Q waves were present in Lead 1, and QS waves in Lead aVL. The T waves were diphasic in Lead 1 and inverted in Leads 2, 3, aVF and V_2 through V_6. The ST segment was slightly depressed in Leads 2, 3 and aVF. The patient continued to be obtunded and died on the fourth postoperative day. Terminally, basal pulmonary rales were audible, and gangrene of the left leg and foot was noted.

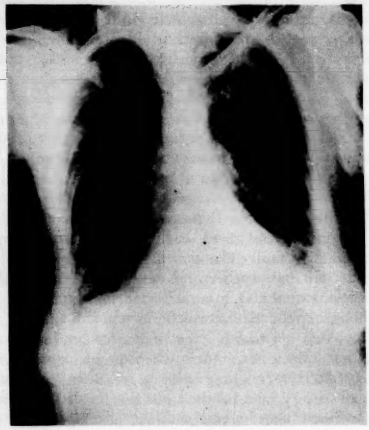

FIGURE 2.

DIFFERENTIAL DIAGNOSIS

DR. BRIANT L. DECKER*: There was evidence from both the history and the x-ray examination that the patient had a large hiatus hernia, but the symptoms had apparently changed a great deal in the year before admission. This change may possibly have been related to the failing heart, but it is much more likely that the episodes of paroxysmal nocturnal dyspnea were precipitated by the attacks of vomiting. It is possible, however, that both were caused by episodes of atrial fibrillation. Finally, she had an episode of partial or possibly complete obstruction of the upper gastrointestinal tract and vomited guaiac-positive material. Of course, as was expected, she was markedly dehydrated both at physical examination and by the battery of laboratory tests. She had pulmonary emphysema and was in moderate congestive heart failure, with cardiomegaly, rapid atrial fibrillation and pleural effusion on the left side. In addition to atrial fibrillation the electrocardiogram showed sagging, depressed ST segments, indicating probably coronary-artery disease with anoxia or possibly hypopotassemia since she had been vomiting a great deal before she received digitalis. She also had peripheral arteriosclerosis. Kidney function seemed good, as shown by the concentration and the rapid excretion of the dye and the rapid return to normal of the nonprotein nitrogen with proper hydration. The white-cell count of 14,900 makes me wonder if there were other causes than the dehydration, such as acute infection, to account for this. She had apparently not lost much blood in the vomitus as shown by the hemoglobin although that also reflected the dehydration. The sputum contained organisms that were potentially dangerous, *H. influenzae, Staph. aureus* and beta-hemolytic streptococcus. May I see the x-ray films?

DR. PAUL M. G. ST. AUBIN:—Three different radiologic studies were carried out on this patient: films of the chest, an intravenous pyelogram and gastrointestinal studies. The series of chest films show an air-fluid level posterior to the heart. The lung fields in the initial film are clear; the heart does not appear enlarged; nor is there evidence of pulmonary congestion on admission. There is no evidence of pleural fluid on the initial study. A small amount of air is seen under the left leaf of the diaphragm. On the next examination, approximately two weeks later, the posteroanterior film of the chest demonstrates a rounded density obscuring the left costophrenic sinus, which certainly has the appearance of fluid (Fig. 1). The lung fields remain clear; the heart is not enlarged, and the pulmonary vessels are not engorged. Five days later fluid is still present on the left, with a little on the right. Rounded densities are now seen in both lower-lung fields (Fig. 2). These densities are rather discrete and are adjacent to the pleural surface. In the gastrointestinal study, the barium passed down the esophagus into the fundus of the stomach and around through the body into the antrum; the duodenal bulb was seen to lie apparently just above the diaphragm fluoroscopically.

DR. DECKER: Do you think the duodenal bulb is below or above the diaphragm?

DR. ST. AUBIN: My impression when I did the fluoroscopy was that the duodenal bulb was above

*Associate physician, Massachusetts General Hospital.

the diaphragm. The plain films of the abdomen do not show much. On the intravenous pyelogram, contrast substance appeared promptly in both renal collecting systems. There is a suggestion of a mass in the region of the lower pole of the right kidney, and the calyceal systems in the lower poles of the right kidney are not seen well. The right ureter seems to be slightly displaced medially. The forty-minute film shows the calyxes of the lower pole of the left kidney to be intact.

DR. DECKER: Did you take any lateral films to try to determine the position of the mass?

DR. ST. AUBIN: Lateral films were not taken.

DR. DECKER: I wonder if you would comment about the density in the right side of the chest. Neither it nor anything suggesting it was present on the initial film. There was an episode that could have been pneumonia or a pulmonary infarction. What do you think about this in relation to either?

DR. ST. AUBIN: It could have been either pneumonia or pulmonary infarction, but since the density lies at the periphery adjacent to the pleural surface and is well demarcated, the episode is more likely to have been an infarction.

DR. DECKER: Although the density does not have the characteristic contour of a healing infarct?

DR. ST. AUBIN: I do not think it is healing; I think it is relatively fresh. It has sharp, rounded margins, — there are actually several of them, — and there is pleural effusion associated with them.

DR. DECKER: Your report is somewhat different from that in the protocol and makes it look less like congestive heart failure than I had first thought.

I shall try first to decide what was going on in the gastrointestinal tract. Before admission there had been no loss of weight. The patient had vomited coffee-grounds material apparently for this first time, and she had had no history of pain. The episodes of vomiting were apparently associated with nocturnal dyspnea. It seems to me that she had an obstruction at or just below the diaphragm. Do you think that the subdiaphragmatic air was in a loop of bowel, or was it free air?

DR. ST. AUBIN: One film shows the fundus and the esophagus, which has slipped back into a relatively normal position under the left leaf of the diaphragm. I suspect that the air is in the fundus of the stomach that has gone back to its normal position.

DR. DECKER: You do not think it is free air under the diaphragm?

DR. ST. AUBIN: I do not know. In this view the tube, as it goes down the esophagus, goes into the abdomen and then back into the chest. The upper portion of the stomach is mobile, and this portion of the hernia reduced relatively easily.

DR. DECKER: Have you a film that shows free air? You believe that the air is in the fundus of the stomach?

DR. ST. AUBIN: I cannot say with absolute assurance, but I assume that it is.

DR. DECKER: The patient had an obstruction of the lower end of the stomach by incarceration of the stomach at the level of the diaphragm, by a lesion in the stomach or possibly by a lesion outside the stomach causing the incarceration. With the change in symptoms during the previous year, the attacks becoming more frequent and lasting longer, I believe that most probably partial obstruction had developed and that the final attack precipitated incarceration of the hernia at the level of the diaphragm. The question also arises whether some lesion in the chest could have produced incarceration. Pleural effusion was not present. I had thought that congestive heart failure might have produced it, but she was apparently not in congestive heart failure on admission. It seems to me that the most likely cause in a person of this age is an ulcer in the prepyloric area of the stomach, probably carcinomatous, which produced obstruction and subsequent incarceration at the diaphragm.

The heart apparently was not large as was thought on admission, and there was no evidence of congestion and no fluid. The patient did have episodes of fibrillation, but apparently, with digitalization, the physicians were able to establish normal sinus rhythm although episodes of fibrillation recurred.

The two episodes — the first after intubation of the stomach with aspiration, when she had a temperature of 103°F., coughing spells, a great deal of vomiting and sticky rales on the right side, and the second a few days later, when she had a temperature of 103°F., with bronchial breathing on the right side, and a white-cell count of 30,000 — strongly suggest that she had a pneumonitis; but the fact that the hematocrit rapidly fell within the two-day interval from 40 to 29 mm. suggests to me that she had a fairly large pulmonary embolus. From the appearance of the films of the chest I should say that she probably had several pulmonary emboli, with resulting pleural effusion.

From the record it seems that she had episodes that were certainly the result of hypopotassemia. During the second episode, when the temperature was 103°F., it was necessary to give her Pronestyl and potassium chloride intravenously, which precipitated heart block. The lack of food, together with the large amount of fluid that she was losing through the upper gastrointestinal tract, made it natural that she should have hypopotassemia. Finally, however, the physicians were unable to sustain her. It was necessary to do a jejunostomy because of the total obstruction, but this did not help much. She continued to vomit and to secrete large amounts of fluid in the stomach. Then there was a sudden fall in the blood pressure and definite changes in the electrocardiogram. She became hyperpneic, disoriented and almost unarousable. It seems to me that at that point she probably had a myocardial infarct. The physicians believed that she may have had a sudden change in the central nervous system, for they did a lumbar puncture. She

may have had embolic phenomena in the brain from the fibrillating atria. She became unconscious, and she had respiratory irregularity, both of which indicate brain damage. Terminally, she had gangrene of the lower part of the left leg. All those could well have been caused by emboli from the atrial fibrillation.

My final diagnoses are ulcer of the prepyloric area, probably malignant, and multiple pulmonary emboli, probably from the legs. She may have had a massive pulmonary embolism, and she may have had emboli to the central nervous system.

DR. JOSEPH W. GARDELLA: What do you think the pelvic mass displacing the ureter was, Dr. Decker?

DR. DECKER: I do not know what it was. It was not mentioned on physical examination; the abdomen was reported as being normal.

DR. ELLIS L. ROLETT: An indwelling catheter was removed from the left femoral vein just before the episode of ventricular fibrillation. At the time this catheter was removed the pulse was regular. The patient was next seen half an hour later in shock. At that time the electrocardiogram revealed ventricular fibrillation for the first time. Therefore, the Service thought that she had thrown a pulmonary embolus at the time of removal of the catheter. We also found that she had fine rales in the right side of the chest at the time she arrived on the Service, and thought that she had a pneumonia from the very beginning. The final diagnosis was hiatus hernia, probably incarcerated. I do not think she had any findings that made us strongly favor a malignant process.

CLINICAL DIAGNOSES

Hiatus hernia.
Aspiration pneumonia.
Coronary-artery disease.

DR. BRIANT L. DECKER'S DIAGNOSES

Incarceration of hiatus hernia.
Malignant ulcer of prepyloric area.
Multiple pulmonary emboli from leg veins.
?Emboli to central nervous system.

ANATOMICAL DIAGNOSES

Paraesophageal diaphragmatic hernia, incarcerated.
Pulmonary embolism, massive, terminal.
Pulmonary infarct, right lower lobe, old.
Paradoxical embolus through patent foramen ovale.
Renal infarct, left.
Thrombosis, iliofemoral veins, bilateral.

PATHOLOGICAL DISCUSSION

DR. AUSTIN L. VICKERY: As Dr. Rolett has implied, the physicians caring for the patient thought that the febrile state was explainable on the basis of aspiration pneumonia as a result of the hiatus hernia. It was also considered that she had a gastric lesion such as Dr. Decker predicted to account for the sudden incarceration of the hiatus hernia, which she had apparently been living with for many years without great difficulty.

At autopsy, a large incarcerated paraesophageal hernia was found with the majority of the stomach in a peritoneum-lined hernial sac, which extended into the left side of the chest and the posterior mediastinum. Its neck admitted four fingers freely. The stomach was twisted on itself, and its lumen was almost totally obstructed. The gastric mucosa was congested, as was that of the esophagus, but no lesion or ulceration was found. In the thorax, there was 75 ml. of bloody fluid in the right side of the chest, and fibrous adhesions bound the lung bases to the diaphragm. The outstanding finding was that of large emboli occluding all major branches of both pulmonary arteries and extending into the periphery of the lung in several of the smaller ramifications. We considered this massive embolism to be the terminal phenomenon. There was bilateral iliofemoral-vein thrombosis, and it is interesting to learn that the removal of a femoral-vein catheter antedated the final episode by the significantly short period of about an hour. The lungs themselves weighed 650 gm. together, which is not particularly heavy, and were unremarkable except for a large infarct in the right lower lobe, which was rust brown, partially necrotic and liquefied, indicating that it had been there for quite a while. I think it is consistent with the febrile course that she had in the previous two weeks. No other infarcts were found in the lungs, but it is possible that she had had other emboli with small infarcts that had healed. The left kidney contained a large, necrotic infarct, and the renal artery was occluded by an embolus. There were no thrombi in the left atrial appendage, which one might expect with atrial fibrillation, to account for the embolus to the kidney. However, there was an interesting incidental finding of a functionally patent foramen ovale, which measured about 0.5 cm. when it was distended to its greatest degree into the left atrium. It is possible then to postulate "paradoxical" embolism from leg-vein thrombi via this arterial shunt. This mechanism may be more convincing in view of the large pulmonary infarct, which, by increasing the pulmonary arterial resistance, could explain a shunt from the right atrium to the left.

We did not find any evidence of significant intrinsic heart disease. There was partial calcification of both the mitral and aortic annulus on an arteriosclerotic basis, and minimal coronary-artery disease.

Examination of the brain was negative. I think that the lumbar puncture was probably traumatic and that the semishock state was the result of general debilitation.

DR. DECKER: What was the mass over the right kidney?

DR. VICKERY: That was a genuine "red herring." Nothing was found there. The "mass" was probably the right lobe of the liver.

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TOBACCO RESEARCH — A REPORT OF PROGRESS

A YEAR ago the *Journal* commented editorially on the appointment of a scientific advisory board to the Tobacco Industry Research Committee. Whereas the Tobacco Industry Research Committee, although "dedicated to the support of the investigation of fundamental matters relating to a connection between tobacco use and human health" represents the industry itself, the Scientific Advisory Board, composed, like a still higher tribunal, of nine eminently qualified persons, is devoted only to the development of scientific knowledge, let the chips fall where they may.

Some confusion may have existed at times in respect to the relation between these bodies, their functions and their loyalties. The Committee, when all is said and done, may logically have the interests of the tobacco industry at heart and may devoutly wish that the great business empire it represents can be cleared of complicity in the ordeal by lung cancer. The Board is interested only in scientific fact and a wise allocation of the funds that the Committee has placed at its disposal.

As was stated in the editorial previously mentioned, evidence that the producers are acting in good faith "is practically guaranteed by the personal reputations of the nine distinguished scientists who have consented to serve on the Scientific Advisory Board to the Tobacco Industry Research Committee and by the recent statement of policy that has been adopted by the Board." This policy, which was accepted by the Committee, guarantees complete freedom of thought and action to scientists receiving grants and approves the initial presentation in accepted medical and scientific journals and before accepted medical and scientific societies of the results of their research.

The Advisory Board, reimbursed only for its time and expenses, except for its salaried scientific director, has defined the scope of interests within which investigations should be sponsored. This scope covers three main areas — the physical and chemical composition of tobacco and its accompanying products, tissue changes in human beings and animals exposed to tobaccos and their derivatives, and a study of habits in relation to tobacco, and the emotional and physical makeup of tobacco users.

Already, between November, 1954, and September, 1955, 54 grants had been made to a total of $1,035,427.37, and a third allocation of $500,000 was announced on February 1 of this year. Most of these grants have been for one year and 22 have already expired; it may be expected that the results of some of the studies should make their appearance in the not too distant future.

The whole setup of this comprehensive investigation indicates that the tobacco empire is now fully aware of its responsibility in the matter and the dis-

tressing implications of any attempts to pass judgment before the trial. The proper role is not that of concealment, if the suspicions now directed down Tobacco Road are substantiated, but that of openly and honestly acknowledging the existence of a toxic factor and trying to eliminate it.

HANS ZINSSER MEMORIAL FUND

LAST summer, fifteen years after his tragic death from lymphatic leukemia, friends, students and former associates of the late Hans Zinsser announced their plan to establish a fund in his memory at the Harvard School of Public Health. When the design was first disclosed, unsolicited gifts in excess of $13,000 had already been received; it is now hoped that at least $100,000 may be raised to serve the contemplated purpose of providing a fund the income of which will be devoted "to purposes in keeping with Dr. Zinsser's deep concern for human health improvement." Since his interests were catholic it is intended that the Zinsser Fund, although administered by the dean of the Faculty of Public Health, will be available for use in any part of the University.

Hans Zinsser, Harvard's distinguished microbiologist, was born in New York City in 1878 and died in Boston in 1940. He received his early education in American and European schools and graduated from Columbia University with the A.B. degree in 1899 and the degrees of M.A. and M.D. in 1903. During the course of his career he was awarded honorary doctorates of science by Columbia, Western Reserve, Lehigh, Yale and Harvard. He served on the Red Cross Typhus Commission in Serbia in 1915 and with the American Expeditionary Force from 1917 to 1919 as Army sanitary inspector and as assistant director of the Division of Laboratories and Infectious Diseases. After a teaching career in bacteriology at Columbia and Leland Stanford universities he came to Harvard in 1923 as professor of bacteriology and immunology, becoming Charles Wilder Professor in 1925, the post that he held until his death.

Dr. Zinsser, in view of his interests and his attainments, may justly be called a broadly related man. As scientist, teacher, humanitarian, musician, author and poet he achieved distinction in each field, and he entered each with zest. Of his major nontechnical writings *Rats, Lice and History,* published in 1935, and *As I Remember Him,* an autobiography written during the two years of his final illness and published shortly before his death, achieved the greatest distinction.

The last lines of his last sonnet have been already long remembered:

> How good that ere the winter comes, I die!
> Then ageless, in your heart I'll come to rest
> Serene and proud, as when you loved me best.

PLATINUM DERMATITIS

LISTS of gifts available for the Yule of 1955, now happily receded into the ranks of past Christmases, were enough to torture the imagination. There was, however, little suspicion, except in dermatologic circles, that several of these amenities were capable also of evoking purely somatic reactions. These hitherto unrecognized dangers were suggested by Sheard,* writing as long ago as March, 1955, in *Archives of Dermatology,* with reference to so common an element as platinum.

Platinum salts, as Sheard states, have long been known to act as skin allergens and even to cause asthma; but only recently has contact with the pure metal been found to result in a dermatitis. This observation may account for the disturbances discovered among those who seem to react unfavorably to dental wiring, as well as in various persons apparently allergic to wedding rings. However, the skin may be protected, the complexion spared and marital relations left undisturbed by the plating of the platinum with rhodium, the rare metal found in platinum ores and characterized by its rose-red salts.

Fortunately, the results of these scientific if devastating observations were concealed in a highly technical journal and did not affect the 1955 trade in Christmas novelties, which were largely concerned with mink, emeralds and platinum. The recipient of an emerald-studded toothbrush with platinum-set mink bristles might be annoyed at learning the source of his rhagades, and the statement could also apply to those whose holiday had been spuriously gladdened with nail files, moustache combs or toothpicks of the same white metal. Whereas last season's prosperity may have justified the fabulous traffic in mink and ermine-covered key rings, diamond-studded shoe trees, emerald-crusted coin purses and pearl-embroidered can openers, the dermatologic risks involved will no longer permit the commercialization of platinum garter clasps, bobby pins or suspender buttons, unless rhodium plated.

The case of the platinum blonde has not yet been discussed by Sheard or, so far as is known, by any other observers.

*Sheard, C., Jr. Contact dermatitis from platinum and related metals: report of case. *Arch. Dermat.* **71**:357-360, 1955.

INTERNATIONAL CONGRESS OF LIBRARIES AND MEDICAL CENTERS

THE proceedings of the International Congress of Libraries held in Brussels last September are significant not only to medical librarians but also to everyone concerned with medical documentation.

The resolutions adopted by the Congress are as follows: that a program be started to instruct medical students in the methods of medical bibliography

and medical documentation; that close co-operation be established with the medical profession for the development and co-ordination of common interests; and that public authorities and international organizations contribute to the payment of shipping costs to facilitate the exchange of publications. To this end, the Congress urges that an international organization be established through the creation of medical sections by national associations of librarians and documentalists.

Physicians, and all others interested in medical writing, will heartily endorse the program proposed by the Congress. An auspicious beginning in its effort to promote effective liaison among medical librarians, and between them and the medical profession, appears to have been made.

Dr. Hutawa states, that he has obtained the happiest results by causing half or one drachm of chloroform to be inhaled every hour, day and night, by patients affected with pneumonia. — Preuss. Verein.

Boston M. & S. J., *March 6, 1856*

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

This year the Committee on Finance has voted to distribute $6,000 to the district societies toward defraying their operating expenses from the surplus in the General Fund at the end of 1955.

Members are reminded that the percentage of this sum that is allocated to their own district is determined by the number of dues from that district paid by March 1, 1956. Members who have not paid their dues by this date are automatically removed from the mailing list of the *Journal* until such dues are paid.

ELIOT HUBBARD, JR.
Treasurer

DEATHS

FELTON — Lester M. Felton, M.D., of Worcester, died on December 25. He was in his fifty-eighth year.

Dr. Felton received his degree from Cornell University Medical College in 1922. He was urologist at four Central Massachusetts hospitals, formerly president of the Worcester District Medical Society and secretary of the Committee on Legislation of the Massachusetts Medical Society, a fellow of the American Medical Association and the American College of Surgeons and a member of the American Urological Association and the New England Urological Association.

He is survived by his widow, two sons and a daughter.

FURBUSH — Leroy C. Furbush, of Saugus, died on February 15, 1955. He was in his sixty-seventh year.

Dr. Furbush received his degree from Middlesex University School of Medicine in 1915. He was a fellow of the American Medical Association, served on the Saugus Board of Health for approximately twenty-one years, and was a former member of the Lynn Hospital Staff.

He is survived by his widow, two daughters and a son.

KURTH — Harold R. Kurth, M.D., of Lawrence, died on February 7. He was in his sixty-first year.

Dr. Kurth received his degree from Harvard Medical School in 1919. He was president-elect and formerly a member of the Committee on Public Relations of the Massachusetts Medical Society, secretary and public-relations councilor of the Essex North District Medical Society, president of the medical staff and chief of surgery at Lawrence General Hospital, a fellow of the International College of Surgeons, the American College of Surgeons and the American Medical Association, an honorary fellow of the International Academy of Proctology and a member of the New England Fracture Committee for the American College of Surgeons.

He is survived by his widow, two sons and a daughter.

GARLAND — Roy Garland, M.D., of Gloucester, died on January 15. He was in his seventy-eighth year.

Dr. Garland received his degree from Harvard Medical School in 1903. He was a former member of the Massachusetts Medical Society.

He is survived by his widow and two sons.

NOONAN — William A. Noonan, M.D., of Boston, died on January 3. He was in his seventy-second year.

Dr. Noonan received his degree from Harvard Medical School in 1909. He was a past president of the New England Society of Anesthesiologists, a member of the American Society of Anesthesiologists and a fellow of the American Medical Association.

He is survived by his widow, three sons and a daughter.

STANLEY — Francis G. Stanley, M.D., of Beverly, died on August 24. He was in his eighty-first year.

Dr. Stanley received his degree from Harvard Medical School in 1909. He was formerly city physician in Beverly.

He is survived by two daughters.

TOBEY — Harold G. Tobey, M.D., of Boston, died on December 26. He was in his seventy-first year.

Dr. Tobey received his degree from Harvard Medical School in 1911. He was formerly a member of the staffs at Harvard Medical School, Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital and Children's Hospital and was a fellow of the American Medical Association and the American College of Surgeons, and a member of the American Otological and Laryngological Society.

He is survived by his widow and two daughters.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

ORTHOPEDIC CLINIC	DATE	CLINIC CONSULTANT
Salem	March 5	Paul W. Hugenberger, M.D.
Haverhill	March 7	William T. Green, M.D.; Henry Banks, M.D.

Brockton	March 8	George W. Van Gorder, M.D.
Gardner	March 12	Carter R. Rowe, M.D.
Lynn*	March 12	Daniel M. Killoran, M.D.; John J. Crowley, M.D.
Pittsfield	March 21	Edward J. Coughlin, Jr., M.D.
Hyannis	March 22	Paul L. Norton, M.D.
Worcester	March 23	John W. O'Meara, M.D.
Fall River	March 26	David S. Grice, M.D.; Arthur W. Trott, M.D.
Springfield	March 27	James D. Fisher, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	March 6, 13, 20, 27
Fitchburg	March 7, 14, 21, 28

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D., and Joseph E. Murray, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

CORRESPONDENCE

SUSPENSION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held January 19, 1956, it was voted to suspend the registration of Dr. Arthur F. Phillips, New London, New Hampshire.

Robert C. Cochrane, M.D., *Secretary*

State House
Boston

BOOK REVIEWS

Hyperostosis Cranii. By Sherwood Moore, M.D. 4°, cloth, 226 pp., with 107 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $10.50.

Dr. Moore has written a detailed monograph covering a wealth of personally reviewed material. The report, however, records too many details without a critical selection of the significant facts. The book would have benefited by better organization and more careful editing of the author's interesting life's work that is included in this book. It is a good book, but hard reading.

Alexander S. Macmillan, Jr., M.D.

Forceps Deliveries. By Edward H. Dennen, M.D. 8°, cloth, 228 pp., with 91 illustrations. Philadelphia: F. A. Davis Company, 1955. $6.50. (*Obstetrics and Gynecology: A series of monographs.* Edited by Claude E. Heaton, M.D.)

In a concise and well organized discussion of forceps deliveries, within the scope of slightly more than 200 amply illustrated pages, Dr. Dennen has produced a manual that should be of great value to the teacher as well as to the student of obstetric art. He describes with great clarity the prerequisites for forceps delivery, discusses the basic or "classic" instruments and points out the advantages and disadvantages of the commonly used modifications of the basic instruments when applied for delivery of the head from the various stations and positions that it may occupy in the birth canal.

In recent years authors of obstetric textbooks, notably Greenhill and Eastman, have adopted a "revisionist" attitude toward the older and essentially standard practice of dividing forceps deliveries into the low, medium and high varieties. Dr. Dennen says, "the long distance from low to mid pelvis and the short distance from mid to high pelvis have led to numerous errors in classification." He therefore proposes to use the biparietal diameter of the head in its relation to the four major planes of the pelvis as an index of the station of the head. Thus, he finds that when the biparietal diameter is in the inlet or superior strait the leading bony point of the head is just above the plane of the ischial spines. When forceps are applied to a head at this level the operation is described as *high forceps.*

When the biparietal diameter lies below the superior strait, with the leading point of the head at or just below the plane of the ischial spines, the head *nearly* filling the hollow of the sacrum, application of forceps is described as *midforceps.*

When the biparietal diameter is at or below the plane of the ischial spines, with the leading point within a finger's breadth of the perineum between contractions, the head completely filling the hollow of the sacrum, application of forceps is described as *low midforceps.*

For low forceps delivery Dr. Dennen postulates that the bony head must be on the perineum between contractions and visible during each contraction. This combination of circumstances, he says, means that the biparietal diameter of the head is judged to be below the plane of the ischial spines, with the sagittal suture in or nearly coinciding with the anteroposterior diameter of the outlet. In this definition Dr. Dennen is in substantial agreement with the definition of low forceps recommended by Greenhill and Eastman, but insistence that the head must be so rotated as to bring the sagittal suture to complete or nearly complete coincidence with the anteroposterior diameter of the outlet leaves this reviewer in doubt about Dr. Dennen's classification of the case in which the bony head is on the perineum between contractions and visible during each contraction with the sagittal suture still oblique or even transverse. The occurrence of such cases is not rare — completion of rotation at a low station followed by extension is all that is required to effect *low forceps delivery;* yet Dr. Dennen would presumably catalogue this type of delivery as a low midforceps.

This criticism, although semantic rather than practical, and not designed to detract from the merits of the author's classification, is pertinent to accurate comparison of figures obtained from different clinics and teaching hospitals.

Dr. Dennen's discussion of the Kielland, Barton and Piper forceps, and of their advantages and disadvantages, is especially timely. Some obstetric services teach the use of one type of forceps that the current chief of staff finds most useful. *No one type is best for all cases,* a fact that this valuable monograph makes abundantly clear.

Thomas R. Goethals, M.D.

Ancient Therapeutic Arts: The Fitzpatrick Lectures delivered in 1950 and 1951 at the Royal College of Physicians. By William Brockbank, M.A., M.D. (Camb.) F.R.C.P. 8°, cloth, 162 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $5.00.

Three ancient therapeutic devices that have come down from time immemorial are the use of the enema for cleaning the bowel, cupping and leeching designed to remove impurities in the blood, and counterirritation as a form of relieving pain. More recently a fourth has been added — namely, the intravenous injection of drugs. Dr. William Brockbank, an English physician, chose to discuss this subject in the Fitzpatrick Lectures delivered in 1950 and 1951 at the Royal College of Physicians in London. These lectures have now been printed, accompanied by an unusual number of splendid illustrations.

To those who are interested in the history of medicine, and to many others, this book is strongly recommended, for no one has previously investigated these subjects so thoroughly or put his research in such a readable form. The book was printed in England, although published in America,

and the publishing is excellent. There is a full list of references to each section, and the text, particularly with the extraordinary illustrations, makes the book an outstanding one.

HENRY R. VIETS, M.D.

Pain: Its mechanisms and neurosurgical control. By James C. White, M.D., and William H. Sweet, M.D. With assistance in the psychiatric sections of Chapters 4 and 10 from Stanley Cobb, M.D., and Frances J. Bonner, M.D. 4°, cloth, 736 pp., with 134 illustrations and 53 tables. Springfield, Illinois: Charles C Thomas, 1955. $17.50.

In the last two decades there has been a growing interest in the treatment of severe pain by surgical intervention. It is only recently that a book devoted to this subject could be compiled, and the authors, leaders in the field, have analyzed the records of over 400 patients suffering from persistent severe pain on whom operation was justified. The patients were seen between 1935 and 1949 except for a few suffering from cardiac pain who were operated on before 1935. The final date for analysis was chosen as 1950, leaving a five-year period for follow-up study of the cases under consideration and thus allowing for complete evaluation of the efficiency of any particular procedure.

The first part of the book deals with the fundamental aspects of pain in the end organs and afferent tracts of the central nervous system. A second part is devoted to a discussion of surgical technics such as nerve block, neurectomy, rhizotomy and the interruption of pain pathways in the spinal cord, medulla and other parts of the nervous system. The final section concerns specific painful conditions such as the neuralgias of the peripheral nerves, amputation stumps, phantom limbs and trigeminal neuralgia. Further chapters consider painful conditions associated with the thoracic viscera, particularly the heart, aorta and lungs, and diseases of the abdominal viscera with pain as a chief symptom. The book includes an extensive bibliography, ample index and good illustrations, and is only marred by a certain amount of repetitious material and some long work sheets printed as attached tables, which should be omitted from future editions. The book is outstanding in its field, and sets a pattern for future development in a relatively new but ever-increasing aspect of the treatment of disease.

HENRY R. VIETS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Cough Syncope. By Vincent J. Derbes, M.D., professor of medicine and director of the Division of Allergy and Dermatology, Tulane University of Louisiana School of Medicine, and visiting physician, Charity Hospital of Louisiana, New Orleans; and Andrew Kerr, Jr., M.D., assistant professor of medicine, Louisiana State University School of Medicine, and visiting physician, Charity Hospital of Louisiana, New Orleans. 8°, cloth, 182 pp., with 7 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $4.75. (Publication No. 231, *American Lecture Series.)*

Communicable Diseases. By Franklin H. Top, M.D., M.P.H., F.A.P.H.A., professor of hygiene and preventive medicine and head, Department of Hygiene and Preventive Medicine, and director, University Department of Health, State University of Iowa, consulting director, State (of Iowa) Hygienic Laboratories, consultant in infectious diseases, University Hospital, and consultant, Communicable Disease Center, United States Public Health Service, Atlanta, Georgia; and collaborators. Third edition. 8°, cloth, 1208 pp., with 109 illustrations and 15 color plates. St. Louis: C. V. Mosby Company, 1955. $18.50.

Swift and Carroll: A psychoanalytic study of two lives. By Phyllis Greenacre, M.D. 8°, cloth, 306 pp., with 7 illustrations. New York: International Universities Press, 1955. $5.00.

New and Nonofficial Remedies: Containing descriptions of the articles which stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1, 1955. Issued under the direction and supervision of The Council on Pharmacy and Chemistry, American Medical Association. 12°, cloth, 653 pp. Philadelphia: J. B. Lippincott Company, 1955. $3.35.

Taschenbuch der praktischen Medizin. Edited by Dr. J. Kottmaier, Baden-Baden. Third edition. 12°, cloth, 1058 pp. Stuttgart: Georg Thieme, 1955. DM 36.- $8.60. (Distributed in the United States by Intercontinental Book Corporation, New York City.)

Talking with Patients. By Brian Bird, M.D., associate professor of psychiatry, Western Reserve University School of Medicine. 12°, cloth, 154 pp. Philadelphia: J. B. Lippincott Company, 1955. $3.00.

Clinical Toxicology. By Clinton H. Thienes, M.D., Ph.D., director, Institute of Medical Research, Collis P. and Howard Huntington Memorial Hospital, Pasadena, California, visiting professor of pharmacology and toxicology, School of Medicine, University of Southern California, attending pathologist (toxicology), Los Angeles County Hospital, and consulting member of staffs of Collis P. and Howard Huntington Memorial Hospital, Glendale Sanitarium and Hospital, Glendale Physicians and Surgeons Hospital, Methodist Hospital of Southern California and Temple Hospital, Los Angeles; and Thomas J. Haley, Ph.D., chief of the Division of Pharmacology and Toxicology, Atomic Energy Project, and associate clinical professor of medicine (industrial medicine), School of Medicine, University of California. Third edition, enlarged and thoroughly revised. 12°, cloth, 457 pp., with 16 illustrations and 33 tables. Philadelphia: Lea and Febiger, 1955. $6.50.

Our Backward Children. By Karl F. Heiser, Ph.D., consultant, League for Emotionally Disturbed Children. 8°, cloth, 240 pp. New York: W. W. Norton and Company, Incorporated, 1955. $3.75.

Saddle Block Anesthesia. By Ray T. Parmley, M.D., director, Department of Anesthesiology, St. Francis Hospital, lecturer in anesthesiology, University of Kansas School of Medicine, staff anesthesiologist, St. Joseph and Wesley Hospitals, and consultant, Veterans Administration Hospital, Wichita, Kansas. 8°, paper, 59 pp., with 9 illustrations and 2 tables. Springfield, Illinois, Charles C Thomas, 1955. $2.50. (Publication No. 258, *American Lecture Series.*)

Clinical Pathology in General Practice: Specially commissioned articles from the British Medical Journal, October 1953 to July 1954. (Fully revised.) 8°, cloth, 321 pp., with illustrations. London: British Medical Association, 1955. 21s.-

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Clinical Biochemistry. By Abraham Cantarow, M.D., professor of biochemistry, Jefferson Medical College; and Max Trumper, Ph.D. Fifth edition. 8°, cloth, 738 pp., with 54 illustrations and 44 tables. Philadelphia: W. B. Saunders Company, 1955. $9.00.

Laboratory Identification of Pathogenic Fungi Simplified. By Elizabeth L. Hazen, Ph.D., associate bacteriologist (mycology); and Frank Curtis Reed, laboratory illustrator and photographer, Division of Laboratories and Research, New York State Department of Health, Albany, New York. 4°, paper, 108 pp., with 22 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $5.50. (Publication No. 253, *American Lecture Series.*)

Transplantation of Tissues: Cartilage, bone, fascia, tendon, and muscle. By Lyndon A. Peer, M.D., clinical and research director, Rehabilitation Center for Plastic and Reconstructive Surgery, St. Barnabas Hospital, Newark, New Jersey. 4°, cloth, 421 pp., with 163 illustrations. Baltimore: The Williams and Wilkins Company, 1955. $13.50.

The Visual Fields: A study of the applications of quantitative perimetry to the anatomy and pathology of the visual pathways. By Brodie Hughes, M.B., B.S. (Lond.), CH.M. (Birm.), F.R.C.S. (Eng.), professor of neurosurgery, University of Birmingham, and surgeon-in-charge, Department of Neurosurgery, United Birmingham Hospitals. 8°, cloth, 174 pp., with 158 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $7.25.

Veterans Administration Technical Bulletins. Series 10. Vol. 7, 1954. Washington 25, D. C.: March, 1955.

Histologische Geschwulstdiagnostik: Systematische Morphologie der menschlichen Geschwülste als Grundlage für die klinische Beurteilung. By A. v. Albertini, professor of pathological anatomy, Universität Zürich, and director of the histologic institute, Universität Zürich. 4°, cloth, 544 pp., with 638 illustrations. Stuttgart: Georg Thieme, 1955. DM 98.40.- $23.40. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Industry and Tropical Health. II. Proceedings of the Second Conference, Industrial Council for Tropical Health Sponsored by the Harvard School of Public Health, April 20-22, 1954, in New York and Boston. 4°, cloth, 266 pp., with illustrations and tables. Boston: Harvard School of Public Health, 1955. $10.00 (professional rate, $5.00).

Experimental Psychology: A series of broadcast talks on recent research. Edited by B. A. Farrell, Wilde Reader in Mental Philosophy in the University of Oxford. 12°, cloth, 66 pp. New York: Philosophical Library, Incorporated, 1955. $2.75.

Hypotension: Shock and cardiocirculatory failure. By Paul G. Weil, M.D., Ph.D., director of Transfusion Service, Royal Victoria Hospital, Montreal, Canada. 12°, cloth, 78 pp., with 9 illustrations. Philadelphia: J. B. Lippincott Company, 1955. $2.25.

Society and Medicine: Lectures to the laity, No. XVII. The New York Academy of Medicine. Edited by Iago Galdston, M.D. 8°, cloth, 131 pp. New York: International Universities Press, Incorporated, 1955. $3.00.

The Pathogenesis of Poliomyelitis. By Harold K. Faber, director of poliomyelitis research, Department of Pediatrics, Stanford University School of Medicine. 8°, cloth, 157 pp., with 16 illustrations and 24 tables. Springfield, Illinois: Charles C Thomas, 1955. $5.00. (Publication No. 257, *American Lecture Series.*)

The Management of Acute Poliomyelitis. By C. P. Stott, S.R.N., C.M.B. (Part I), Diploma of Poliomyelitis Nursing (U.S.A.); and M. Fischer-Williams, M.R.C.P.Ed., senior neurologic registrar, Birmingham United Hospitals. With a foreword by W. Ritchie Russell, C.B.E., M.D., F.R.C.P.Ed., F.R.C.P.Lond., consultant neurologist, United Oxford Hospitals. 8°, cloth, 99 pp., with 43 illustrations. Edinburgh: E. and S. Livingstone, Limited, 1955. $3.00. (Distributed in the United States by the Williams and Wilkins Company, Baltimore.)

Medical Problems of Old Age. By A. N. Exton-Smith, M.A., M.D. (Cantab.), M.R.C.P., physician, Whittington Hospital, London. With a foreword by The Rt. Hon. Lord Amulree, M.A., M. D., F.R.C.P. 8°, cloth, 331 pp., with 117 illustrations. Bristol: John Wright and Sons, Limited, 1955. $7.00. (Distributed in the United States by the Williams and Wilkins Company, Baltimore.)

Virus and Rickettsial Diseases. By S. P. Bedson, M.D., D.Sc., F.R.C.P., F.R.S.; A. W. Downie, D.Sc., M.D., professor of bacteriology, University of Liverpool; F. O. MacCallum, B.Sc., M.D., director, Virus Laboratory, Central Public Health Laboratory; and C. H. Stuart-Harris, M.D., F.R.C.P., professor of medicine, University of Sheffield. Second edition. 8°, cloth, 407 pp., with 34 illustrations. Baltimore: The Williams and Wilkins Company, 1955. $6.75.

Erläuterungen zu den Strahlenschutznormen für medizinische Röntgeneinrichtungen, -anlagen und Röntgenschutzkleidung DIN 6811, 6812 und 6813: Im Auftrage des Fachnormenausschusses Radiologie im Deutschen Normenausschuss in Arbeitsgemeinschaft mit der Deutschen Röntgengesellschaft. By Dipl.-Ing. H. Graf and Dr.-Ing. A. Schaal, Erlangen. 8°, paper, 92 pp., with 10 illustrations. Stuttgart: Georg Thieme, 1955. DM 8.70.- $2.10. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

NOTICES

ANNOUNCEMENT

Dr. Harold D. Levine announces the removal of his office to 1180 Beacon Street, Brookline 46, Massachusetts, for the consultation practice of cardiology.

SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, March 20, at 12 noon.

Dr. Saul C. Holtzman will speak on the subject "Organ Neuroses." All physicians are invited to attend.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Children's Medical Center and the Boston City Hospital in the Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, March 12, at 8 p.m.

PROGRAM

Children's Medical Center, Benedict F. Massell, M.D., presiding:

Aortic Stenosis in Children. Patrick A. Ongley, M.B., Ch.B. (N.Z.), and Alexander S. Nadas, M.D.

Present Status of Hormone Therapy of Rheumatic Fever and Carditis. S. B. Roy, M.D., J. W. Dow, M.D., R. J. Walther, M.D., E. Zervopoulos, M.D., E. Young, M.D., and B. F. Massell, M.D.

Chronic Catheterization of the Renal Artery of the Dog: A new technic for the study of renal function. Abraham M. Rudolph, M.D., A. Clifford Barger, M.D., and Stanley M. Rokaw, M.D.

Boston City Hospital, Laurence B. Ellis, M.D., presiding:

The Clinical Interpretation of Brachial-Artery Pressure Tracings. Ernest W. Hancock, M.D., Walter H. Abelmann, M.D., and Rhett P. Walker, M.D.

Nature's Circulation Experiments. James W. Dow, M.D., and Sujoy B. Roy, M.D.

The Clinical Value of Pulmonary-Function Tests in Patients with Heart Disease. Walter H. Abelmann, M.D., Asher Marks, M.D., and David W. Cugell, M.D.

Free parking privileges are available on the premises at Science Park (emergency telephone number, RI 2-1410).

Interested physicians and medical students are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

March 4–8. College of Medical Evangelists Postgraduate Convention. Page 347, issue of February 16.

March 5 and April 2. Fried Lecture Series. Page 535, issue of September 22.

March 5–28. Consultation Clinics for Crippled Children in Massachusetts. Page 440.

March 5, 19, April 2 and 16. Hartford Medical Society. Page 242, issue of February 2.

March 6. Phi Delta Epsilon Fraternity Graduate Program. Page 347, issue of February 16.

March 6. Forum on Rehabilitation. Page 399, issue of February 23.

March 6, 13, 20, 27 and April 3. Boston City Hospital House Officers' Association. Page 297, issue of February 9.

March 7. Massachusetts General Hospital. Page 347, issue of February 16.

March 12. New England Cardiovascular Society. Page 443.

March 13. Yale University School of Medicine. Page 347, issue of February 16.

March 15–17. American Orthopsychiatric Association. Page 86, issue of January 12.

March 19–21. Josiah Macy, Jr., Foundation Lectures. Page 400, issue of February 23.

March 19–22. American Academy of General Practice. Page 1092, issue of December 15.

March 19–28 and June 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

March 20. South End Medical Club. Page 443.

March 21. New England Pediatric Society. Page 347, issue of February 16.

March 21, 22 and 23. Medical and Dental Symposium. Page 348, issue of February 16.

March 21 and April 25. Massachusetts Heart Association. Page 623, issue of October 6.

March 21 and April 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

March 24 and 25. American Psychosomatic Society. Page 260, issue of August 11.

March 28 and April 18. Greater Boston Medical Society. Page 208, issue of August 4.

April 3. Third Microcirculatory Conference. Page 399, issue of February 23.

April 4. New England Surgical Society. Page 347, issue of February 16.

April 15–17. American College of Allergists. Page 399, issue of February 23.

April 16–21. American Academy of Pediatrics. Page 399, issue of February 23.

April 23–26. International Academy of Proctology. Page 399, issue of February 23.

May 2. Postgraduate Medical Institute. Page 487, issue of September 15.

May 3–5. American Goiter Association. Page 348, issue of August 25.

May 28–June 1. European Symposium on Vitamin B. Page 578, issue of September 29.

June 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.

June 21–24. American Academy of Dental Medicine. Page 944, issue of December 1.

August 19–23. American College of Chest Physicians. Page 840, issue of November 10.

September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.

September 10–14. American Dietetic Association. Page 1180, issue of December 29.

Calendar for the Week Beginning Thursday, March 8

Thursday, March 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m. Guest Speaker of the Bingham Associates. Medical and Surgical Aspects of Portal Hypertension. Dr. Charles G. Child, III. Cape Cod Hospital, Hyannis.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*11:15 a.m. Thoracic Conference. Some Aspects of Congenital Heart Disease. Dr. Alexander S. Nadas. Main Amphitheater, Peter Bent Brigham Hospital.

*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.

*12:00 m.–1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.

*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

Friday, March 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.

*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.

*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

Saturday, March 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.

*9:30–11:00 a.m. Surgical House Officers' Conference. Second Floor Conference Room, Carney Hospital, Dorchester.

*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, March 12

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.

*12:00 m.–1:00 p.m. Medical Conference. Stearns Auditorium, New England Center Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

(Concluded on page xxviii)